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# **The Uppers and Downers of Drug Development**

**Why do some drug projects succeed in development while others fail? An exploration into the conditions associated with the success and failure of UK rare cancer drug projects**

Philippa Crane

PhD Science and Technology Policy Studies

SPRU, University of Sussex

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## **Abstract**

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The organisation of drug development has radically changed in the last 40 years due to changes in the scientific knowledge base and the availability of new forms of finance. Stimulated by breakthroughs in biotechnology, new investment has facilitated changes to the strategies and structure of the industry. Furthermore, scientific advances have provided greater understanding of disease, drug targets and disease-drug interactions, particularly in oncology. Yet new ways of organising innovation bring new challenges. This thesis provides evidence to inform new policies and business models by assessing the non-technical conditions associated with the success and failure of drug development projects. The thesis presents an integrative theoretical framework that supports a multi-dimensional analysis of the network, organisation and individuals involved drug projects. This approach is applied to case studies of 11 development projects for rare cancer drugs involving UK organisations. These cases are then compared and contrasted through a descriptive multi-case analysis and a Qualitative Comparative Analysis.

The findings contribute towards an understanding of the environmental conditions for the successful development of drugs. Firstly, the concept of project drag is introduced, to draw attention to the accumulation of issues during development that can cause projects lose momentum and lead to termination. The organisational environment around firms is found to be key; common disruptions are identified, particularly within small firms which are more vulnerable to industrial dynamics than larger organisations. This thesis also highlights mechanisms that can mediate adverse conditions; key individuals, their networks, power and consistent enthusiasm for projects can mediate project drag. The thesis also makes a methodological contribution in the formation and operationalisation of an integrative framework for project evaluation which provides a foundation for further research in this area. The thesis is concluded with policy recommendations of pathways that contribute towards the successful development of drug projects.

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## Abbreviations and Acronyms

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AC – American Cyanamid

ALL – Acute Lymphocytic/Lymphoblastic/Lymphoid Leukaemia

AML – Acute Myeloid Leukaemia

AZ – AstraZeneca

BTG – British Technology Group

BW – Burroughs Wellcome

CAT – Cambridge Antibody Technology

CLL – Chronic Lymphocytic Leukaemia

CML – Chronic Myeloid Leukaemia

CRC – Cancer Research Campaign

CRT – Cancer Research Technology

CR-UK – Cancer Research UK

DNA – Deoxyribonucleic Acid

EMA – European Medicines Agency

EU – European Union

FDA – Food and Drug Administration

GSK – GlaxoSmithKline

GvHD – Graft vs. Host Disease

HCC – Hepatocellular Carcinoma

HCL – Hairy Cell Leukaemia

HTS – High Throughput Screening

ICR – Imperial Cancer Research

IND – Investigational New Drug

IPO – Initial Public Offering

KSB – KS Biomedix

Mab – Monoclonal Antibody

M&A – Mergers and Acquisitions

MRC – Medical Research Council

NCI – National Cancer Institute

NDA – New Drug Application

NINDS – National Institute of Neurological Disorders and Stroke

NHL – Non-Hodgkins Lymphoma

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

NIH – National Institutes of Health

NSI – National Systems of Innovation

ODA – Orphan Drug Act

(cs/fs)QCA – (crisp-set/fuzzy-set) Qualitative Comparative Analysis

RA – Rheumatoid Arthritis

R&D – Research and development

RCC – Renal Cell Carcinoma

STS – Science and Technology Studies

TAC – Technology Antibody Centre

VC – Venture Capital

WHO – World Health Organisation

# 1 Introduction

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## 1.1 Aim

This thesis considers new therapeutics as one of the most powerful avenues for addressing global disease burden. It follows that this work will contribute towards furthering an understanding of the process by which therapeutic drugs are developed. There has been great success in reducing mortality associated with infectious diseases, however, cancer remains a significant challenge for drug innovation.

In 1900 tuberculosis, gastrointestinal infections and pneumonia/influenza collectively accounted for 539.3 deaths in per 100,000 people per year in the USA, cancer mortality stood at 64/100,000. In 2010, due to the effects of increased diagnosis and an aging population, cancer accounted for 185.9 per 100,000 and pneumonia and influenza stood at 16.2 per 100,000 (Jones et al., 2012). However, cancer patient survival (UK) has improved from 24% in 1970, to 50% in 2010 (Cancer Research UK, 2014)), demonstrating the benefits of earlier diagnosis and the availability of effective drugs.

In investigating the development of therapeutics to aid diseases we pose the question: what influences the success of drug innovation in cancer? This can be addressed in a variety of ways, with many assuming that a lack of market incentives explains disparity between disease classes, while researchers involved in drug discovery and development may conclude that the underlying issue is a lack of drug target or disease pathology understanding. In order to understand these mechanisms and facilitate policy debate, this thesis will explore a holistic approach to appreciating the social and economic issues surrounding drug development. This will facilitate an in-depth analysis exploring the interdependencies of the conditions that differentiate success from failure.

To achieve this, we take drug projects as the unit of analysis and investigate the non-technical conditions contributing towards the success or failure. We define non-technical failures as projects terminated for reasons not associated with safety or severe efficacy (i.e. when no patient responses are seen in trials). The focus of this thesis is the development stages of drug innovation (i.e. once in clinical trials) and will not investigate the conditions influencing the outcome of discovery phases, although these early stages will be discussed in the chronological assessments of the drug case histories. To assess the perception that markets are the root cause of a lack of drug development, rare cancers are taken as the focus of this thesis. This will allow for inferences to be made in the increasingly important area of personalised medicine, where drugs are produced for stratified patient populations.

## **1.2 Why Cancer Therapeutics? Motivations for this Research**

There are three main justifications for focusing on cancer drug development: firstly, the debilitating nature of the disease and public health burden caused; secondly, the need to understand the process of developing drugs in the wake of shifts and changes to the scientific understanding of cancer and industrial changes that have characterised the past 40 years; and finally, the declining productivity of the industry and increasing costs of drug development, while cancer has, at the same time, become a major focus in the sector.

Cancer arises from an abnormal growth of cells resulting from the accumulation of mutations in genes controlling cell function (Scotting, 2010). Traditionally cancer has been categorised in terms of its symptomatic locality i.e. breast, colon, lung etc., where primary cancers are associated with the position of the initial tumour, and secondary cancers are described upon metastasis. It is this secondary phase that is the most prevalent cause of mortality due to the interference with multiple organs in the body (Tobias and Hochhauser, 2014:1). However, more recently advances in the genetic and molecular understanding of the pathology of cancer facilitate diagnosis based on the genetic causation<sup>12</sup>.

Cancer is treated with one, or a combination of approaches, including surgery, radiation, and therapeutics. Historically approaches centred on cutting out tumours (surgery), burning target cells to shrink tumours (radiation) and poisoning rapidly dividing cells affecting both tumour and normal cells (cytotoxins/chemotherapy) (Gerber, 2008, Corrie, 2008). Scientific advances in the understanding of the cause of cancer have facilitated a different strategy, of specifically targeting cancer cells, with the aim of reducing the toxicity of chemotherapeutics<sup>3</sup> (Corrie, 2008, DeVita and Chu, 2008, Gerber, 2008).

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<sup>1</sup> [www.who.int/genomics/public/geneticdiseases/en/index3.html#Cancer](http://www.who.int/genomics/public/geneticdiseases/en/index3.html#Cancer)

<sup>2</sup> Definitional issues associated with cancer have arisen from criticisms of the 'overdiagnosis' and 'overtreatment' of cancers that result from mass screening programmes and the subsequent diagnosis of tumours that may not otherwise have caused harm to the patient. This is linked to the genetic categorisation of cancer subtypes, a pattern that has been described as 'splitting' (as opposed to 'lumping' based on shared genetic mutations causing diseases in other areas) (Hedgecoe 2004). In response to these issues Esserman and colleagues (2013) suggest that cancer should be redefined only to include malignant growths, or lesions found in the body 'with responsible likelihood of lethal progression if left untreated'.

<sup>3</sup> Chemotherapeutics are commonly described as analogous to cytotoxic agents that characterised therapeutic options until recently.

These shifts in treatment strategies illustrate the different operational principles<sup>4</sup> that have been used in the fight against cancer.

The first justification for choosing cancer is the severity of the health burden it causes. Cancer is one of the leading causes of death worldwide with 8.2 million cancer deaths in 2012 (World Health Organisation (WHO), 2014) with incidence set to increase from 10 million new cases globally in 2000 to an estimated 15 million in 2020 (Duenas-Gonzalez et al., 2008).

Another motivation for focusing on oncology<sup>5</sup> is that it is the most advanced example of personalised (targeted) therapeutics aimed at particular patient subgroups defined by molecular and genetic analysis. This was clearly shown in statistics from 2012 whereby cancer drugs occupied the largest portion of personalised therapeutics (33%) reviewed by the FDA (US Food and Drug Administration, 2013). It follows that studying the development of cancer drugs, which can imply small patient sizes due to population stratification, facilitates the application of findings more widely, for instance in rare diseases and personalised medicine.

The investigation, into the mechanisms associated with successful therapeutics development, is also justified by the industry productivity crisis that has occurred recently. Although not observed in orphan or cancer drugs, where numbers have increased, the annual development of new chemical entities (NCEs) has declined over the past three decades (Grabowski and Wang, 2006). In fact, the pursuit of high risk disease areas, by the industry, has been observed to play a significant role in the declining productivity over the past decade (Pammolli et al., 2011).

The high costs of the discovery and development of drugs in general, with estimates standing at around \$800m (but ranging between \$500m to \$1bn) (Adams and Brantner, 2006, DiMasi et al., 2003), motivates a need to understand the process in greater detail. In particular, the production of drugs in oncology has been highlighted as being one of the most expensive therapeutic areas (after respiratory diseases) standing at an average of \$1,042m (Adams and Brantner, 2006). It is likely that this increase in cost is, in part, associated with the increase in duration of trials, a trend observed over the past 3

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<sup>4</sup> Operational principles were described by Polanyi in 1958, as being the rules that govern the use of implements in technology. Discussed further in Chapter 2, section 2.2.5.

<sup>5</sup> The terms oncology and cancer will largely be used interchangeably, where oncology is the study of cancer (<http://www.cancer.net/navigating-cancer-care/cancer-basics/cancer-care-team/types-oncologists>)

decades (Kaitin and DiMasi, 2011), which is, in turn, likely to be associated with the increased interest in central nervous system and anti-neoplastic<sup>6</sup> (largely cancer) drug research. The productivity crisis is further discussed in Chapter 2.

Therapeutics, as opposed to diagnostic, surgical, or other treatment innovations have been selected as an area of interest because it provides the thesis with a clear context within which complex dynamics can be assessed. Furthermore, therapeutics span the complex world of different sectors, i.e. private and public, representing an interplay between science and technology. In addition, particularly in cancer, therapeutics are a popular treatment pathway, particularly for treating inaccessible tumours, which are not easily removed through surgery, and those that have metastasised, and are therefore distributed and most dangerous.

Drug policies, such as orphan drug designation, fast track and accelerated approval, and compassionate use programmes (discussed in Chapter 2), also make therapeutics an interesting avenue for research because they are impacted by incentives that have been implemented in an attempt to encourage innovation. By implementing an in-depth analysis of drug discovery and development this thesis will contribute towards additional policies to address the fundamental issues associated with drug innovation, in cancer, rare diseases, and personalised medicine.

This thesis emphasises the determinants of success (and failure) as defined by a drug achieving (or not) regulatory approval. This is, perhaps, controversial due to contemporary debate that it is not the rate of innovation<sup>7</sup> that should be encouraged, but the diversity, direction and distribution of innovation that is important (Stirling, 2009). However, this thesis feeds into a context of unmet clinical need, severe disease burden and mortality in patients afflicted by diseases that have no, or little, treatment options.

The development of cancer therapeutics is an example of medical innovation, which is characterised as an atypical representation of innovation dynamics. Here, the science-based nature of the industry is being increasingly emphasised wherein innovation is

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<sup>6</sup> A neoplasm is defined as ‘an abnormal mass of tissue that results when cells divide more than they should or do not die when they should’ ([www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=46264](http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=46264)). This definition includes both benign and malignant growths, but when used in the context of drug research, due to the lack of drug research expected in benign growths, can be taken to be akin to oncology therapeutics research.

<sup>7</sup> This debate resonates with the idea that not all innovation contributes towards societal benefits. This is particularly salient in discussions of regulation in drug innovation, whereby questions over the innovative value of new products are often raised.

reliant on scientific advances and understanding (Pavitt, 1984). As demonstrated in Chapter 2, the changing nature of the science on which drug innovation is based is necessitating an adjustment to the industry, and system, responsible for technological change in this area. Cancer is at the forefront of this change, whereby targeted therapeutics present the most progressive example of personalised medicine. We therefore seek to inform and infer to emerging modalities of drug innovation and address issues associated with the productivity crisis.

### **1.3 Chapter Outline**

This thesis begins with an outline of the empirical context of the research. Here, Chapter 2 highlights the context of drug development in cancer therapeutics from an historical perspective. This Chapter emphasises the dynamics of drug development, particularly in cancer therapeutics, and the shift towards a process based on scientific understanding of disease. In response to this shift the industrial environment surrounding the development of therapeutics has adapted.

A systematic review of the biomedical innovation literature is presented in Chapter 3. This Chapter discusses the key influences defining the progression, and success, of innovation. In doing so we discuss the actors involved in drug innovation, their characteristics, and the nature of influence they have. Much of the literature is limited to discussions of one or two dimensions of actors, i.e. individuals, organisations and networks, necessitating the use of a framework in this thesis to address these different levels.

Two key gaps are identified in the literature, firstly the lack of studies taking a multidimensional approach, and secondly the need for a better understanding of influences on innovation at the project level. This Chapter also identifies conditions influencing innovation, on the multiple dimensions highlighted. From this a framework is constructed in which four conditions, namely knowledge base and accumulation, market demand, stakeholder perspectives and organisational environment, will be discussed.

The methodological approach and research design will be presented in Chapter 4 providing justification for the implementation of a multiple case study approach. This draws on Eisenhardt's (1989) theory building process, integrating Ragin's Qualitative Comparative Analysis (QCA) method (Ragin, 1987, Ragin, 1989, Ragin, 2000).

Chapter 5 provides a pair of model cases of well-documented path-breaking drugs (one small molecule and one biologic) to demonstrate the framework to be applied in Chapters

6 and 7. Each case history is presented using a consistent framework set out in Chapter 3.

The projects for analysis were identified using case selection criteria as follows: the project had to have had i) involvement from a UK organisation during development; ii) either succeeded (i.e. file for approval) or failed (i.e. be discontinued post-phase II); iii) between the years 1999-2010; iv) have a primary indication (as per the Pharmaprojects database) defined as a 'rare' cancer (both in US and UK), and v) be of a relevant therapy type (discussed more in section 4.4.2.2).

Projects originating in large pharmaceutical firms (pharma) are presented in Chapter 6 and projects from smaller biotech<sup>8</sup> and academia are presented in Chapter 7. Chapter 8 outlines the QCA procedure and interpretation of this. Finally, Chapter 9 will provide the discussion and contributions of the thesis.

#### **1.4 Contributions**

This thesis reveals a series of features of drug development. Firstly, that organisational environment is a key contributor to both success and failure. Secondly, that issues accumulate in a process of project drag. Finally, that key individuals can act to overcome the accumulation of these issues.

The first major contribution of this thesis is the particular significance of the organisational environment surrounding the project, both for successful and unsuccessful drugs. Here, a supportive organisational environment is a necessary condition for the successful development of a project, and a sufficient condition in combination with other conditions. Here, while all successful projects need a supportive organisational environment, some, despite having this support, still fail. Furthermore, a lack of supportive organisational environment also plays a key role in contributing towards failure via project termination.

This thesis will argue that project success and failure can also be differentiated depending on the size of the developing firm. In general, projects undergo a process of project drag throughout development, whereby issues ('downers') lead to a loss of momentum. In successful projects mechanisms are implemented to overcome these

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<sup>8</sup> 'Biotechnology' firms, or biotech, has become a generic term used to describe any small therapeutics firm working in therapeutics that was founded post-1980, rather than those that are specifically involved in the development of drugs using biological methods.



(‘uppers’). In failed projects, however, downers accumulate to cause eventual project termination.

In large firms projects are insulated to some extent, from ‘downers’ e.g. from the action of external industrial dynamics. However, in small firms, vulnerabilities to environmental issues such as a lack of funding mean that the project has external pressures placed on it. In addition, we observe that, in small firms, there is the additional creation of protected spaces. Protected spaces occur when projects developed with involvement from small firms are shielded from the influence of project drag due to the shared expectations surrounding drug development. This acts to either suspend evaluation or lower thresholds for decisions-making. Due to external dynamics often necessitating M&A or licensing agreements, protected spaces breakdown and re-evaluation of the project is undertaken. Where issues were previously seen as conquerable, re-evaluations can lead to the uncovering of project drag and the subsequent termination of drug development.

In addition, this thesis finds that key individuals with effective abilities in promoting a project, utilising their networks and enthusiasm, positively influence project outcomes. Here, the action of such individuals can contribute towards overcoming issues causing project drag.

Methodologically, this thesis makes a contribution in the development and operationalisation of a framework to study facilitate a multi-dimensional (organisational, individual and network) perspective on the progression of drugs, from discovery to approval or discontinuation. Furthermore, we develop and implement a theory building protocol incorporating a systematic multiple case study comparative analysis.

The literature review undertaken in Chapter 3 highlights the previous biomedical innovation literature and the consistent focus on the organisation as the unit of analysis. By focusing on innovation as mediated by the organisation, this approach overemphasises the potential for inferring innovation trends from organisational dynamics. In contrast, this thesis takes the project as the unit of analysis and thereby assesses the innovation at the core, with consideration of the actors, individuals, organisation, and networks, influencing innovation. This is particularly important due to the multiplicity of the organisations involved in innovation, particularly, as will be demonstrated, in the development of drugs.

Much of the literature focuses on either large firms or small firms, and their innovative characteristics and tend to highlight the factors associated with success rather than failure. This thesis fills these gaps comparing innovative practices in large firms with

those of smaller firms, and seeks to learn from the differences between the factors leading to success and those that impact failure, assuming the two outcome have different causal pathways.

## **1.5 Research Questions**

This research is primarily concerned with the nature of the drug innovation process (both in discovery and development stages), and the relationship between factors that influence innovation and the outcome of that innovative process. To address this aim of the thesis three research questions were posed:

- 1) Why do some drug projects succeed in development, while others fail?

The first research question is purposefully broad, setting out the main directive of the research, to investigate the 'why' behind drug innovation. It also defines the unit of analysis, applying the definition of innovation in a particular way, centring on the output rather than the techniques or knowledge systems. Due to the breadth of this research question further development, in additional research questions, is required.

- 2) What environmental (socio-economic) conditions, identified from the innovation literature, influence go/no-go decisions in drug development?

The second research question refers to the construction of the framework, from the biomedical innovation literature, which will be used to focus the collection of data and the analysis of that data for the purposes of this thesis.

- 3) How do the environmental (socio-economic) conditions, identified from the framework, contribute towards the development of rare cancer drug projects? Do these conditions show interactions and/or cumulative causality (project drag)?

The final research question addresses the main substance of this thesis. It builds on the previous objective, of finding a suitable framework for studying therapeutic drug innovation, delving further into the kinds of findings the research will ascertain. The focus of this is to understand *how* conditions contribute towards decision making in drug discovery and development, i.e. how environmental factors affect the actions of the firm, and the knock-on effect this has on specific projects. This question also considers the possibility of factors being interactive and/or potentially cumulatively causal, i.e. contributing towards increasing problematic scenarios which eventually lead to termination.

## 2 Context of Cancer Therapeutics and Drug Development

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### 2.1 Introduction

This Chapter focuses on the history of drug development with a particular emphasis on cancer research providing the necessary background to understand the case histories that follow (Chapters 7 and 8). There are four key themes that comprise this Chapter. The first is the demonstration of the evolution of an increasing interest in cancer research over the period discussed. Secondly, during the same period we witness a shift in the approach to drug discovery and development, in the technological modalities used. This has led to a strategic and structural shift in the industry, mainly involving the introduction of biotech firms as a new business model and the shift towards nichebusters and orphan drugs. Finally, these changes have also been witnessed in the regulatory environment surrounding drug development, which has encouraged and incentivised the rise of drugs to fill unmet need in rare diseases.

As demonstrated in this Chapter, there is recognition that the system surrounding biomedical innovation has witnessed a shift over the past 40 years. These shifts are characterised by changing operational principles which, in cancer treatment, has led to a shift from blockbusters to targeted therapeutics. Operational principles are the rules governing the use of artefacts in technology (Polanyi, 1958) arising in response to changes in science leading to new problems (e.g. different knowledge of disease). In innovation operational principles are generated and selected between to solve identifiable problems (Yaqub, 2008).

In early cancer therapy surgery was the dominant operational principle, where cutting out the tumour was the main treatment option. This was followed by strategies to burn, in the form of radiotherapy, and poison tumours cells, using cytotoxins. Contemporary approaches, enabled through the increase in scientific understanding of cancer disease pathology and drug targets, centre on targeted therapeutic strategies. These operational principles represent a general shift in drug discovery and development, from broad brush, to targeted (personalised medicine), strategies relying on a range of scientific knowledge.

In addition, shifts, from 'blockbusters'<sup>9</sup> to 'nichebusters'<sup>10</sup> (Dolgin, 2010, Kumar Kakkar and Dahiya, 2014), from general to personalised medicine (Ginsburg and McCarthy,

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<sup>9</sup> The term 'blockbusters' has been adopted as a description of drugs that reach over US\$1bn in revenues (Booth and Zimmel, 2004)

<sup>10</sup> Nichebuster is used to describe the rise in interest in drugs aimed at small patient populations.

2001), and from cytotoxic to targeted oncology therapies (Duenas-Gonzalez et al., 2008)<sup>11</sup> have been conceptualised as paradigm shifts, drawing on the literature on scientific and technological paradigms by Kuhn (1962) and Dosi (1982).

Dosi's (1982) premise, building on Kuhn's (1962) scientific paradigms, was that while 'technological paradigms'<sup>12</sup> maintained stability, 'technological trajectories' (i.e. the direction these problem solving activities took) are subject to selection pressures<sup>13</sup> differentiating the options available. Despite Dosi's (1982) focus on a technology from a societal perspective we will utilise the same concept on a project level accounting for the actors and selection pressures surrounding that project and exploring the relevant operational principles.

In observing the action of paradigm shifts it is necessary to appreciate the path dependency of the system surrounding innovation, and its role in constraining change, resulting in stability. For instance, the new wave of approaches based on biotechnology is the result of a shift in science, constrained by what has gone before, which limits its 'revolutionary' potential (Nightingale and Martin, 2004, Hopkins et al., 2007). In this, despite the introduction of biotechnology leading to the use of new tools and approaches, there are complementarities with older processes, rather than displacement (Pisano, 2006). This has led to increasing complexity in drug development, both in the technologies used, the changes to the organisational structure of the industry and the relationships between the relevant stakeholders (Pisano, 2006).

This increasing complexity, in the increasing reliance on scientific and multidisciplinary knowledge and the changes in system surrounding drug development necessitates an in-depth investigation into the processes at work. This thesis aims to do this by firstly exploring the historical context of the scientific, technological and systemic shifts, and secondly, in Chapter 3, delving more deeply into the effects these shifts have had on the innovation process.

In order to trace the evolving history of the shifts in drug discovery and development this Chapter is subdivided into two main sections: the first explores the historical context of

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<sup>12</sup> Dosi (1982) defined 'technological paradigms' as collections of procedures designed to deal with particular problems.

<sup>13</sup> Dosi (1982) observes that selection pressures may be non-economic, technological, social, institution, or economic.

drug development prior to 1970<sup>14</sup>, the second highlights the post-1970 developments, distinguished due to the differences in technologies and trends present pre- and post-1970 (Pisano, 2006:22-38).

The first, pre-1970, section illustrates how an increasing focus on drug discovery and development, by policy-makers, scientists, industry and the public, led to post-war (1940-1960s) successes in the production of cancer therapeutics. In particular we see the formation of institutions for medical research, developments in industry, regulation, and funding, both in the UK, Europe and USA, to be significant in paving the way for cancer research.

The post-1970s period, signifying the biotech era and in the wake of Nixon's War on Cancer, has witnessed the coevolution of a shift in scientific understanding of disease pathology, new technologies, regulation, and industry structures and strategies. As demonstrated, this has paved the way, in cancer research, for a change in paradigm, from poisons (cytotoxins) to targeted (molecular) therapeutics, producing a new age of innovative drugs.

## **2.2 Setting the Scene: Pre-1970s Drug Development**

### **2.2.1 Scientific Research and Healthcare Systems**

Cancer research was not at the forefront of medical research in the early 1900s. At this time life expectancy was low and medical interest centred on the major threat of infectious diseases (Porter, 2002). At this time cancer treatment was largely limited to surgical procedures (Mukherjee, 2011), however, throughout the 20<sup>th</sup> Century the development of the healthcare system and the formation of institutions to support medicine facilitated the development of cancer research and new therapeutics. Furthermore, the political, social and economic unrest in the first half of the 20<sup>th</sup> century contributed towards a promotion of the role of medicine in European and North American science policy. This was characterised by a shift from a 'mission-oriented' model to a reliance on the progression of basic research for technological development (as published in Vannevar Bush's *Science the Endless Frontier*) (Mukherjee, 2011).

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<sup>14</sup> These time periods represent a shift in the way science interacts with the development of drugs, largely in the shift from random screening to discovery processes based on molecular biology, and the associated shifts in industry this motivated

#### 2.2.1.1 USA Health Legislation and Institutions

The National Institutes of Health (NIH) in the USA was established in 1930 (Austoker, 1988:165). Additional State support for medical research came in 1944 as part of the Public Health Service Act, which prompted the NIH grants programme (increasing funding from around \$4m in 1947 to \$100m in 1957). Furthermore, the 1944 Public Health Service Act also led to the authorisation of the NIH to conduct trials, thereby facilitating publicly funded clinical research programmes (ibid).

The 1940s also saw the establishment of several key institutes in the US, facilitating research in mental health, dental diseases, and heart disease (Harden, 2015). In addition, the increasing interest in cancer, its causal factors and the development of technologies motivated the signing of the 1937 National Cancer Institute Act leading to the creation of the NCI, which was 'designed to coordinate cancer research and education' (Austoker, 1988:166, Mukherjee, 2011). The NCI was a key institution for oncology, promoting it as a scientific endeavour by securing public resources for research (Austoker, 1988).

#### 2.2.1.2 UK Legislation and Institutions

In the UK advances in legislation and in the development of a coordinated National Health Service facilitated a platform for drug research and clinical investigation. Institutional changes to the medical system began with the 1911 National Insurance Act, creating a national fund for medical research. In addition, 1913 saw the establishment of the Medical Research Council (MRC) and the Ministry of Health was created in 1919 (coinciding with a budgetary increase in funds for the MRC) (Valier and Timmermann, 2008). The National Health Service, founded in 1948 (Quirke and Gaudillière, 2008, Valier and Timmermann, 2008), built on these medicine-, and health-related initiatives, laying the foundation for a cohesive health system which facilitated patient access to treatments and clinical research.

Charitable organisations focusing on cancer research also appeared early on in the 20<sup>th</sup> century, with the Imperial Cancer Research Fund established in 1902, and the British Empire Cancer Campaign (later Cancer Research Campaign) following 21 years later. However, in the 1930s concerns were raised over the efficiency and effectiveness of the cancer research efforts. This further exemplified in a Daily Herald article in 1932 which stated: 'a large part of the £100,000 being spent in this country on cancer research is wasted because of the jealousies and conflicting ideas and theories held by doctors and scientists' (Austoker, 1988: 151).

In 1939 the UK emulated the US (the 1937 National Cancer Institute Act), introducing the British Cancer Act in 1939, which emphasised the provision of cancer services over research (Austoker, 1988:170). Support for research in the Cancer Act was reportedly purposefully neglected due to a lack of interest from the medical profession and the responsibility for cancer research falling to voluntary cancer organisations (ibid). This resulted in difficulties in the UK cancer research environment which was not comparable to the USA federal cancer programme.

This lack of enthusiasm from the medical profession for cancer research reflects a 'discord' whereby 'perceptions and aspirations of scientists diverged from those of clinicians' (Austoker, 1988:29-31). In response, the post-war secretary of the MRC, Walter Morley Fletcher, publically stated the need to link pathology with other scientific disciplines such as biochemistry, physiology, cytology, virology and immunology, further supporting this with the provision of funding (Austoker, 1988:87).

### **2.2.2 Cancer Research and Animal Models**

In cancer research Bush's premise, that basic science was a key driver for technology, manifested in the investigation into the causal factors involved in human tumours (Austoker, 1988:91-138). This work, and that of the production and testing of therapeutics, was facilitated by the development of animal tumour models. Building on the work of Ehrlich, who identified animal models as a necessary preliminary testing regime for new drugs, the first transplantable rodent tumour system was developed in the 1910s allowing for the screening of large numbers of chemical compounds (DeVita and Chu, 2008, Mukherjee, 2011).

Transplantable models continued to be central to the development of cancer therapeutics until around 30 years ago (Caponigro and Sellers, 2011). The differentiation between animal models and human disease variants is a key consideration in the implementation of this testing regime (Yaqub, 2008, Stroh et al., 2014). Therefore the technological advances in the ability to transplant human tumours to test drugs is a key development in cancer research.

In addition leukaemia and lymphoma screens provide another key research tool. By 1949 this technology had developed sufficiently for the NCI to adopt, as a primary screen for cancer therapeutics, a versatile screening system in the form of a murine leukaemia induced by a carcinogen, Leukaemia L210 (DeVita and Chu, 2008, Caponigro and Sellers, 2011). Leukaemias and lymphomas were important in the development of cancer therapeutics, as they provided a key early stage preclinical model. Their suitability

comes from their sensitivity to a variety of agents (Keating, 1997), stemming from a high proportion of dividing cells, in contrast to the solid tumour equivalent (Pratt and Ruddon, 1979). This is likely to be the reason for the trend towards the development of therapeutics in haematological malignancies more readily than in solid tumours<sup>15</sup>.

### **2.2.3 Public Perception of Cancer Research**

Despite the advances made in oncology from the 1930s to the 1950s there remained a high level of scepticism surrounding the clinical utility of chemotherapy in treating cancer (DeVita and Chu, 2008). The early 20<sup>th</sup> Century saw cancer research develop a reputation akin to quack medicine due to frequent fraudulent claims. It was not until the 1930s that 'respected scientists entered this far from reputable field' (Austoker, 1988:179).

This included Sidney Farber, a pathologist working in a Boston Children's Hospital in the 1930s, who was credited with discovering the first antifolate. Farber worked with Mary Lasker, a former American socialite and later founder of the Lasker Foundation with a particular interest in cancer, to overcome the negative perception of cancer research (Mukherjee, 2011).

Lasker's ambition was to make cancer a public issue and realised that to do this she required the expertise of a scientist (ibid). Farber and Lasker met in 1948, introduced by John Heller, Director of the NCI at the time. Together they developed a mission to bring cancer to the forefront of US politics and gain a level of commitment comparable to that of the Manhattan Project, a strategy that was novel for science policy in biomedical research in the 1950s (Mukherjee, 2011).

In the 1960s medical oncology did not exist as a clinical speciality and those that were involved in chemotherapy treatments were regarded as 'under-achievers' and 'talking of curing cancer with drugs was not considered compatible with sanity' (DeVita and Chu, 2008). This perception was in response to the pessimism caused by the failure of early cytotoxins (e.g. alkylating agents and antifolates) to produce lasting remissions in patients in the 1950s (ibid). Furthermore, at this time drugs for cancer were considered to be poisons, where treatment involved a balance between administering enough to eradicate tumour cells without killing the patient (DeVita and Chu, 2008, Mukherjee, 2011).

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<sup>15</sup> The popularity of using haematological malignancies as a therapeutic indication also comes from the ease of assessing the drugs activity through the action of biomarkers in the blood, something that is more challenging in the case of solid tumours.



Farber used his experiments and successes with antifolates<sup>16</sup> as evidence to support the idea that cancer could be treated with chemotherapeutic agents without understanding their mechanism of action (ibid). Farber and Lasker also homogenised cancer into a single therapeutic area, thereby conceptualising it as a widespread and worldwide problem demanding a specific science policy response (Mukherjee, 2011).

Pressure from Lasker and Farber led to the US government providing \$1m in 1954 for the specific purpose of developing drugs to treat cancer. However, in the wake of slow progress Lasker lobbied for further support and funding was increased to \$5m, coinciding with the development of the Cancer Chemotherapy National Service Center in 1955 (DeVita and Chu, 2008). In 1966 the Cancer Chemotherapy National Service Centre became part of the NCI, renamed the Developmental Therapeutics Program (DTP), and by 1974 had an annual budget of \$68m.

By 1974 the DTP was a major producer of the transplantable tumours derived from mice models and had a programme of screening that could analyse over 40,000 compounds per year, at which point the pharmaceutical industry filled the gap in clinical research in cancer therapeutics by recognising the emerging market for drugs in this area (DeVita and Chu, 2008).

#### **2.2.4 Early Industrial Production of Drugs**

Industrial production of drugs began in the late 19<sup>th</sup> Century with the establishment of a number of chemical companies in the USA and Europe (Porter, 1999:449). This stemmed from a key conceptual shift, namely Paul Ehrlich's 1872 suggestion of the potential for 'magic bullets'. The hypothesis proposed was that the body was made up of receptors which could be interfered with using chemical agents to treat disease (Pisano, 2006:22, DeVita and Chu, 2008, Mukherjee, 2011, National Cancer Institute, 2014). Despite this ground breaking hypothesis the lack of analytical tools to aid drug discovery and development, based on an understanding of human diseases, presented a barrier to the development of such compounds (Pisano, 2006:22).

However, the development of technologies to administer drug compounds, and the discovery of active ingredients by searching for, and isolating, natural substances, did motivate the production of therapeutics (Porter, 2002, Porter, 1999). This led to drug discovery and development efforts based on random screening of natural and

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<sup>16</sup> Antifolates were one of the first chemotherapeutic cytotoxins discovered to treat cancer. This will be discussed further in section 2.2.7.

synthesised compounds for therapeutic effectiveness, and the period 1950s to 1960s being described as the 'golden age' of productivity (Martin et al., 2009). As a result large firms developed chemical libraries of screened compounds, leading to substantial barriers to entry for new firms due to the time and investment required to compete (Pisano, 2006:84).

In addition, economies of scale in experimentation were reached in large firms (Nightingale, 2000). Due to the reliance on random, 'trial and error' drug discovery, economies of scale, in the ability to produce more molecules for experimental use, gave a higher probability of finding a drug that would be sufficiently safe and efficacious to be marketed and profitable (Malerba and Orsenigo, 2002).

It was the volume of experimentation associated with this approach, that promoted the development of larger firms, relying on substantial chemical library and laboratory facilities (della Valle and Gambardella, 1993). However, while economies of scale were realised in large firms, economies of scope in drug discovery and development, which relied on the accumulation of disease- and pathway-specific knowledge, were harder to establish (Malerba and Orsenigo, 2002).

### **2.2.5 Development of Regulatory Policy**

Regulation is key to drug development as approval by a regulatory body is required for all prescription drugs used to treat patients. The major regulatory agencies relevant to this thesis are the Food and Drugs Administration (FDA) in the USA and the European Medicines Agency (EMA) in Europe. The historical development of these institutions has facilitated drug development, due to the risk mitigation enabled through the formalisation of regulation.

For instance, the initial development of the FDA came in response to the Elixir Sulfanilamide tragedy where 107 people died from being administered an antibacterial which caused kidney failure in patients. The resultant Food, Drug and Cosmetic Act (1938) established the requirement of a New Drug Application (NDA) to indicate a drug's composition, safety test results and manufacturing processes. However, at this time, the regulatory process did not ensure patient safety because applications were automatically approved if the NDA was not reviewed within 60 days of submission<sup>17</sup>. This requirement

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<sup>17</sup> [www.fda.gov/oc/ohrt/history.shtml](http://www.fda.gov/oc/ohrt/history.shtml)

was aimed at improving competition and encouraging the industrial production of pharmaceutical drugs.

There was little change to this approach by the FDA, until the 1962 Kefauver-Harris Amendments, which, in response to the thalidomide tragedy<sup>18</sup>, required for safety and efficacy tests to be undertaken. This led to the increased time and costs associated with waiting times for approval and a subsequent decline in productivity in the industry during the 1960s<sup>19</sup>.

### **2.2.6 Cancer Therapeutics (1900-1971)**

The flurry of research during the early half of the 20<sup>th</sup> century led to a flood of new medicinal products by the 1960s. As Porter writes:

‘If before 1900 the contents of the pharmacopoeia were useful largely, if at all, as placebos, by the 1960s a cornucopia of truly effective drugs had emerged out of the twentieth century laboratory: antibiotics, anti-hypertensives (beta-blockers) to prevent strokes, anti-coagulants, anti-arrhythmics, anti-histamines, anti-depressants and anti-convulsants, steroids, such as cortisone against arthritis, bronchodilators, ulcer cures, endocrine regulators, cytotoxic drugs against cancers, and other besides.’(Porter, 2002:107)

In particular, developments in the environment surrounding cancer therapeutic development i.e. research, institutions, industry and policy, led to some successes from the 1940s to the 1970s. Cytotoxin cancer drugs produced at this time were based on the idea that the characteristics of rapidly dividing cells could be interfered with using poisons. The lack of specificity of these drugs, and the resultant effect they had on normal cells led to high levels of toxicity and unwanted side effects.

At this time drug discovery and development approaches were largely serendipitous, however, at least nine key technological approaches and families of compounds were developed: 1) alkylating agents, 2) antifolates, 3) antipurines, 4) antipyrimidines, 5) platinum-based compounds, 6) hormone-based therapies, 7) antibiotic, 8) vinca alkaloids,

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<sup>18</sup> Thalidomide was introduced by a West German pharmaceutical firm in 1957 and was taken as a sleeping aid and to alleviate morning sickness in pregnant women. However, it transpired that the drug caused foetal damage that led to truncated limbs in thousands of new borns and drawing widespread media attention (<http://www.fda.gov/oc/history.html>). The thalidomide is one of the key medical tragedies of the 20<sup>th</sup> Century, causing crippling malformations in over 10,000 babies PORTER, R. 2002. *Blood and Guts: A Short History of Medicine*, London, UK, Penguin Books Ltd..

<sup>19</sup> <http://www.fda.gov/oc/history.html>

and 9) prodrugs. These particular examples have been chosen for their continuing significance in cancer treatment in modern medicine, and for their relevance to further discussions in this thesis.

#### 2.2.6.1 Alkylating agents

War has surprising spillovers in the development of certain technology areas, including in the treatment of cancer. In World War I soldiers affected by the chemical weapon, nitrogen mustard gas, were found to have skin oedemas, ulceration, blindness and respiration problems (Joensuu, 2008). However, in 1919 further investigations found survivors had anomalies in bone marrow, indicating interaction between the compound and lymphoid tissue (Pratt and Ruddon, 1979, Mukherjee, 2011). It was not until the 1940s that these observations became significant.

In World War II, two events converged in the research of nitrogen mustard, later contributing to the conclusion that the compound could be used in treating cancer. Firstly in 1942, in the wake of research carried out in a related compound, sulphur mustard, nitrogen mustard was tested for activity as an antitumour (Pratt and Ruddon, 1979). Secondly, in 1943 a ship containing large amounts of nitrogen mustard was blown up at Bari Harbour in Italy (Pratt and Ruddon, 1979). Survivors were found to have unusual burns, the cause of which went undiagnosed due to wartime secrecy, leading to the deaths of 13% of those exposed (Pratt and Ruddon, 1979). However, later research concerning the Bari incident showed that the gas had the effect of depleting white blood cells in bone marrow and blood plasma (DeVita and Chu, 2008, Mukherjee, 2011). This was discovered in 1943, however results were not published until 1946 (DeVita and Chu, 2008, Mukherjee, 2011).

The discovery that nitrogen mustard acted in depleting white blood cells indicated potential for it to be used as an anti-leukaemia, and anti-lymphoma agent. Research into nitrogen mustard at this time resulted from a transatlantic collaboration between the ICR and Yale University (The Institute of Cancer Research, 2014). This paved the way for the family of compounds referred to as alkylating agents, such as chlorambucil, busulphan, and cyclophosphamide, which remain common in cancer treatment today (DeVita and Chu, 2008, National Cancer Institute, 2014, The Institute of Cancer Research, 2014, Pratt and Ruddon, 1979).

### 2.2.6.2 Antifolates

Antifolates, antipurines and antiprimidines all make up the antimetabolite class of compounds. These act to interfere with DNA production in cells by imitating the metabolites necessary for cell division (Pratt and Ruddon, 1979).

Farber's<sup>20</sup> discover of the anti-folates was motivated by his unwillingness to accept the poor prognosis commonly fated to young patients with leukaemia at this time (Miller, 2006). Inspired by an account of the application of folic acid to stem sarcoma growth in mice, Farber had the idea of treating leukaemia with folic acid (first synthesised in 1937) (Pratt and Ruddon, 1979, DeVita and Chu, 2008, Mukherjee, 2011).

By working closely with the biochemist Dr Yellapragada SubbaRow, at Lederle Laboratories (then part of American Cyanamid) who was producing isolated forms of folic acid and could therefore produce sufficient quantities of the compound (Pratt and Ruddon, 1979, Mukherjee, 2011, Miller, 2006), Farber tested his theory by running a trial treating children suffering from leukaemia with folic acid (Mukherjee, 2011). This had disastrous results; folic acid was found to accelerate leukaemia. However, by discovering that folic acid was key to leukaemia cell growth Farber predicted that an antagonist of folic acid, a compound that SubbaRow later synthesised, could show promise for the treatment of acute leukaemia (Farber et al., 1948, Miller, 2006, Pratt and Ruddon, 1979).

Despite this breakthrough, when the first anti-metabolite<sup>21</sup> of folic acid, aminopterin, was developed and tested in the late 1940s/early 1950s results were found to be short-lived. Subsequent to promising *in vitro* and *in vivo* preclinical work, aminopterin was found to produce an effect in children with acute leukaemia, with a report in 1948 indicating that 10 out of 16 patients treated showed 'unquestionable' but temporary remissions (Farber et al., 1948, DeVita and Chu, 2008, Mukherjee, 2011). These results were met with scepticism, disbelief and outrage from the scientific community due to the rarity of any type of remission (temporary or otherwise) in patients with leukaemia (Miller, 2006).

In response to the high toxicities in this and other trials, a less toxic, more efficacious derivative of aminopterin was developed, called amethopterin, which replaced

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<sup>20</sup> This is, incidentally the same Sidney Farber who collaborated with Mary Lasker to promote cancer research as a policy priority (section 2.2.5)

<sup>21</sup> An anti-metabolite is a molecule that inhibits normal metabolism. In this case the anti-folate inhibits the normal metabolism, and therefore function of folic acid.

aminopterin in clinical practice (Pratt and Ruddon, 1979). This compound is still commonly used today to treat several tumour types as well as autoimmune diseases.

### 2.2.6.3 Purines

In 1944 in an industrial laboratory owned by Burroughs Wellcome, George Hitchings began working with Gertrude Elion on synthesising substances to inhibit the breakdown of purines (components involved in the synthesis of DNA) (Garfield, 1989, DeVita and Chu, 2008). Advances in sulphonamides, which prevented the growth of bacteria, inhibiting the formation of folic acid required for the synthesis of precursors of DNA and RNA<sup>22</sup>, stimulated Hitchings and Elion to pursue an interest in the interference of nucleic acid (the building blocks of DNA) production<sup>23</sup>.

Hitchings formulated a hypothesis similar to that used by Faber, i.e. that cell growth could be interfered with by applying compounds that were slightly different to those that naturally occurred<sup>24</sup> (Garfield, 1989). Hitchings and Elion also proposed that cancer cells divided at a faster rate than healthy cells, thereby paving the way for antimetabolites (i.e. compounds that interrupted DNA replication) (Strebhardt and Ullrich, 2008).

Through this initial interest in developing an understanding of the metabolism of DNA, Hitchings and Elion's research took the form of a programme for chemical synthesis and the development of a biological reference system, in parallel (Hitchings and Elion, 1954). These streams of research led to the development of a series of experimental purine analogues that could then be tested in animal leukaemic models (Pratt and Ruddon, 1979).

By 1951 Hitchings and Elion had adapted these experimental drugs and produced two clinical candidates, 6-thioquanine and 6-mercaptopurine (6-MP), found to be active in human leukaemia (DeVita and Chu, 2008, Pratt and Ruddon, 1979, Garfield, 1989). Despite the work of Hitchings since being observed as being conceived as a "fishing expedition" in the eyes of fellow academics (Mukherjee, 2011), the aim was in fact to make drug discovery more rational<sup>25</sup> and less 'hit and miss' (Koenig, 2006).

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<sup>22</sup> <http://www.drugs.com/drug-class/sulfonamides.html>

<sup>23</sup> <http://www.chemheritage.org/discover/online-resources/chemistry-in-history/themes/pharmaceuticals/restoring-and-regulating-the-bodys-biochemistry/hitchings--elion.aspx>

<sup>24</sup> This approach, i.e. the use of analogues, involved the administration of a molecule with a slight chemical different to a substrate which naturally occurs. In doing so, the analogue binds to the cell receptors and therefore inhibits the action of the target pathway.

<sup>25</sup> The rational drug design approach will be discussed in more detail in subsequent sections

#### 2.2.6.4 Antipyrimidines

5-FU, the first anti-pyrimidine to be discovered, was the first drug developed aimed at non-haematological malignancies (DeVita and Chu, 2008). In a similar analogue-led research pathway, to that of the antifolates and the purines, anti-pyrimidines were developed to inhibit the action of uracil, another key compound in DNA synthesis (Pratt and Ruddon, 1979). This hypothesis came after it was observed by Heidelberger and colleagues that rat tumour cells used radiolabelled uracil more readily than normal cells (Grem, 2000, DeVita and Chu, 2008). This provided a distinction between tumour cells and normal cells, so in 1957, an analogue, 5-fluorouracil was synthesised to target this pathway (Grem, 2000). Since this time, developments have been made in understanding anti-pyrimidine mechanisms of action, for instance, it is now known that 5-FU inhibits thymidylate synthase which in turn inhibits DNA synthesis and interferes with DNA repair (Grem, 2000).

#### 2.2.6.5 Platinum-based compounds

The 1960s saw the development of platinum-related anti-mitotic compounds for cancer treatment (Scriabine, 1999a, Kelland, 2007). The discovery of the anti-tumour potential of platinum-based molecules arose out of biophysics experiments attempting to investigate the influence of electromagnetic radiation on cell division (Kelland, 2007). When platinum electrodes were used in experiments of *E.coli*, Barnett Rosenberg, at the Michigan State University, discovered that upon activation of the field, electrolysis products from the platinum electrodes caused the bacteria cells to misshapen (Kelland, 2007).

These products were subsequently tested in mice carrying transplanted tumour models, and found to cause tumour regression. Trials in humans were carried out by the US National Cancer Institute (NCI) in the 1970s and the drug was approved by the FDA in 1978 (Kelland, 2007). Many platinum-based products are still used in chemotherapy today, particularly in the treatment of testicular and ovarian cancers (ibid). Examples of platinum-based compounds are: cisplatin, oxaliplatin and carboplatin.

#### 2.2.6.6 Hormone therapies

In the late 19<sup>th</sup> Century it was noted that the administration of the hormone oestrogen had effectiveness in women suffering from breast cancer (DeVita and Chu, 2008). Based on these early observations Huggins and Clark, in the late 1930/early 1940s, found that castration, or administration of oestrogen, in dogs led to shrinking of the hyperplastic prostate gland (Pratt and Ruddon, 1979). Hormone therapies are still commonly used in

a number of solid tumours today, for instance, tamoxifen and luteinising hormone blockers in the treatment of breast cancer<sup>26</sup>

#### 2.2.6.7 Antibiotics

The use of antibiotic agents to treat cancer are, like nitrogen mustard compounds, considered to be related to the effort surrounding World War II, involving the screening of fermentation products to isolate and produce antibiotics (DeVita and Chu, 2008). The successful development of actinomycin D, the first antibiotic anti-cancer agent, is attributed to Sidney Farber, who, in 1954, tested the compound, isolated from *Streptomyces*, in paediatric Wilm's tumours (Pratt and Ruddon, 1979). This discovery led to the development of a number of antibiotic anti-tumour drugs, including mitomycin, mithramycin, bleomycin, daunorubicin and Adriamycin, which have been found to be effective in a variety of tumour types (Pratt and Ruddon, 1979, Scriabine, 1999a).

#### 2.2.6.8 Vinca alkaloids

The periwinkle plant had been used in folk medicine for centuries and was, therefore, the subject of isolation and screening (Pratt and Ruddon, 1979, Scriabine, 1999a). This led to the production of the vinca alkaloids. In testing, Noble and colleagues showed that the isolated compound caused bone marrow suppression and later, Johnson and colleagues found antileukaemic activity in mice models (Pratt and Ruddon, 1979). Two major vinca alkaloids are still used in chemotherapy treatment regimens for leukaemias and lymphomas today, namely vincristine and vinblastine (Pratt and Ruddon, 1979, Scriabine, 1999a).

#### 2.2.6.9 Prodrugs

Prodrugs are therapeutics that are administered in an inactive state and activated in the patient, ideally in or around the tumour site (Utku, 2011 ). The contemporary approach to prodrugs in anti-cancers began in the 1950s highlighting the potential for drugs to be made up of compounds that are inert ex-vivo but subsequently activated in the body leading to a therapeutic outcome (Albert, 1958, McKeown et al., 2007, Singh et al., 2008). These types of drugs began to be recognised as an avenue for targeting tumour cells, overcoming issues associated with cytotoxic drugs that tend to show little specificity and can therefore lead to high levels of toxicity in patients (Singh et al., 2008).

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<sup>26</sup> <http://www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/hormone/what-hormone-therapy-is#breast> (accessed April 2015)



In order for prodrugs to be targeted, a mechanism of activation would need to be identified, such as the nature of the tumour environment. As cancer research has enabled an understanding of the factors that can be used to activate drugs, the prodrug approach has increased in popularity. For instance, the hypoxic (lack of oxygen) nature of the tumour environment, for certain types of tumour has been utilised in the case of banoxantrone (see Chapter 7).

#### 2.2.6.10 Chemotherapy Strategies

In order to address the high levels of toxicity of chemotherapy regimens, the 1960s and 1970s saw an increasing trend towards implementation of a strategy to combine cytotoxic agents (Pratt and Ruddon, 1979, DeVita and Chu, 2008, Mukherjee, 2011). The rationale behind this was that the levels of cytotoxic agents in the body could be increased by administering more than one type, thereby increasing remission, while maintaining manageable levels of toxicities, which may be different for different agents (DeVita and Chu, 2008, Mukherjee, 2011).

An additional strategy for chemotherapy that was implemented at around the same time was the use of adjuvant therapeutics, whereby surgery, which was perceived to be the only ultimately curative measure, would be accompanied by a cytotoxic chemotherapy in order to lessen the risk of metastasis of the primary tumour.

#### 2.2.6.11 Conclusion

A change in the scientific understanding of disease (specifically in oncology) requires the generation of a new operational principle. For instance, in prodrugs, by knowing what conditions are present in the tumour environment, or within the tumour, it is possible to develop a drug to activate *in vivo* and therefore target specific cells. The following section will demonstrate how an increase in the understanding of cancer pathology and the appreciation of the role of genetic mutations in the abnormal growth of cells, has enabled the development of new operational principles to target tumour cells without affecting normal cells, so as to reduce the effect of toxicity and adverse reactions.

### **2.3 Contemporary Drug Development 1970-present**

So far this Chapter has discussed the system (institutions, organisations, funding and regulation) that surrounded the development of drugs pre-1970. We witnessed a gradual increase in interest in cancer research, with some successful drugs being produced from a largely serendipitous approach to drug discovery. In this section we further demonstrate the evolution of this system and the shifts not only in the technological

modalities used in the production of drugs, but also the industry and regulatory changes that have accompanied these.

This section will focus on trends in drug development since 1970, providing context for the emergence of new, targeted cancer therapeutics. A key development in the 1970s cancer research was the declaration of the ‘War on Cancer’ by President Nixon in 1971 (Mukherjee, 2011). Motivated in part by the action of Lasker and Farber, this saw a commitment, by the US Congress, to address the public’s call for a concerted effort in researching and developing mechanisms to fight a disease that was becoming an increasing public health problem. As Nixon’s speech puts it:

“The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dreadful disease. Let us make a total national commitment to achieve this goal.” (Nixon, 1971)

In the wake of the 1971 National Cancer Act, oncology saw a significant influx of money whereby the funding of the NCI alone more than tripled in the years 1971-1979 (from \$230m to \$940m) (Bazell, 1998:11). This increased funding was not sufficient to overcome the perception of cancer research as a ‘scientific backwater’, explored by researchers motivated by the sudden surge of interest in the area (ibid). However, 1973 did see the formal recognition of medical oncology as a subdiscipline (Keating and Cambrosio, 2007).

The status of cancer research as a political priority did have the benefit of providing funding for public initiatives, such as the Special Virus Cancer Program in the 1960s and 1970s which was initiated with the purpose of identifying viruses that cause cancer (DeVita and Chu, 2008).

The 1970s saw a turnaround involving an increased interest in cancer, met with the coevolution of scientific understanding of disease pathology, new technologies, regulation and industrial structures and strategies. In addition, the post-1970s period was defined by the rapid development of medical oncology and protocols associated with clinical trials, also accompanied by the establishment of a number of institutions and initiatives to support cancer research both in the USA and Europe (Keating and Cambrosio, 2007). These acted to promote cancer research and the shift from poisons (cytotoxins) to targeted therapeutics. Furthermore, this period is characterised by an increase in competitive environment for organisations involved in drug development. This is demonstrated in the following section.

### **2.3.1 Drug discovery and development**

With the convergence of technologies and science since 1970, there has been shifts in the approaches to drug discovery and development, based on the increasing importance of scientific understanding; of diseases, drug targets and their interactions.

These advances, in experimental technologies, and increasing biochemical and pharmacological knowledge, developed through the 1960s and 1970s, facilitated a more rational approach to drug discovery (rational drug design) (Adam, 2005, Hopkins et al., 2007). This was first exemplified by James Black in his work on the beta-blocker, propranolol, whilst at Imperial Chemistry Industries (later AZ) in the 1960s (Adam, 2005, Hopkins et al., 2007, Hill, 2012:12). This discovery came from a process involving experiments guided from cumulative knowledge of the disease, target and potential compounds that would be active (Hopkins et al., 2007).

The production of drugs using increasingly rational approaches to specific diseases was more widely adopted in the 1970s, further facilitated by advances in genetics, genomics, functional genomics and proteomics, that contributed towards a wealth of knowledge about genes, genetic causes of disease and therefore drug targets (Nightingale, 2000, Hopkins et al., 2007). This was encouraged by the development of DNA sequencing techniques (e.g. by Sanger in the mid-1970s) and the establishment of the Human Genome Project in the late 1980s/early 1990s (completed in 2001)<sup>27</sup> which sought to sequence the entire human genome. However, in this process, genomics has been said to have simply shifted the bottleneck from the identification and production of drugs against specific targets, to the biological characterisation of targets and their relationship to disease (Hopkins et al., 2007).

Furthermore, the 1970s also saw the development of hybridoma<sup>28</sup> techniques. As well as contributing towards the use of monoclonal antibodies (mabs) as therapeutics, hybridoma technology facilitated the production of volumes of antibodies, enabling the study of molecules as targets, and the large scale production of proteins (Hopkins et al., 2007).

Technologies such as these, and others, such as high-throughput screening and combinatorial chemistry, serve both to simplify and complicate research strategies in drug discovery and development (Orsenigo et al., 2001). Simplification occurs because

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<sup>27</sup> <http://www.genome.gov/12011239>

<sup>28</sup> Hybridoma technology involves the production of a hybrid cell lines through the combination of antibody-producing cell (lymphocyte) and a non-antibody producing cancer cell (usually myeloma) or lymphoma cell, thereby facilitating the continuous supply of specified monoclonal antibodies (discussed further in section 2.3.5.4).

alternative routes and hypotheses can be selected in accordance with disease, drug and target knowledge. However complications arise out of the multiplicity of options afforded to different trajectories (Orsenigo et al., 2001).

Genetic advances, particularly in pharmacogenomics, also helped to increase understanding around the heterogeneous nature of patient populations, leading to preclinical safety and increased effectiveness of early stage trials (Hopkins et al., 2007). In addition, in some cases this information has helped to 'rescue' drugs that would have otherwise been deemed inefficacious, because they were found to show responses in only a subset of patients (ibid).

Despite the advances and shifting trends facilitated by the rise in scientific understanding of drugs, targets and diseases, and their interactions, the influence of biotechnology has, until very recently, been disappointing compared to expectations (Nightingale and Martin, 2004, Hopkins et al., 2007). This is demonstrated to be partly due to the increased complexity it has introduced into the process, but also the distance between experimental models (cell cultures) and patients (Hopkins et al., 2007). Another explanation, of the disparity between the vision and reality of biotechnology, is that it over-hyped, whereby the technology never had the opportunity to live up to expectations (Nightingale and Martin, 2004, Hopkins et al., 2007).

### **2.3.2 Regulatory Environment and Incentives**

Recognising the demands of new approaches to drug development, regulation post-1970 saw both a tightening up and move to incentivise the development of drugs for diseases of small populations and with unmet need. Declining productivity (approval rates) of new products, caused by increasing waiting times and costs, motivated the introduction, in 1983, of the Orphan Drug Act. This was followed by the Prescription Drug User Fee Act in 1992 which, through the introduction of user fees for organisations applying for drug marketing approval, allowed the FDA to speed up the drug approval process for human drugs and biological products<sup>29</sup>. This Act specified that the FDA was required to review an application within 12 months of submission for standard reviews (for drugs similar to those already on the market), and 6 months for priority applications (for drugs that represent some novelty in offering advances when compared to available treatments) (Lipsky and Sharp, 2001).

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<sup>29</sup> <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm144411.htm>

Prior to this applications were reported to take between two and eight years to review<sup>30</sup> and 70% of medicines were first approved outside the USA causing a concern in the US industry<sup>31</sup>. More recently regulatory changes have included the 1997 Modernization Act which introduced the fast track policy, industry guidance and post-marketing studies<sup>32</sup>. However, the increased processing rates of regulatory bodies has been controversial. For instance, one critique is that this acceleration has resulted from corporate pressure leading to a lowering of drug standards (Abraham, 2008).

The ethical principles for clinical research were introduced on an EU level with the Declaration of Helsinki in 1964. This was followed, in 1965 by a requirement, of the authorisation of medicinal products prior to marketing in Europe<sup>33</sup>. In the 1970s emphasis was placed on European harmonisation of the approval process, beginning with an introduction of a standardised way of summarising key characteristics of authorised products (in 1983) and a requirement that consultation with an EU level committee should precede authorisation by individual country's regulatory bodies (1987).

In 1990 a centralised procedure for human and veterinary medicinal products was agreed throughout the EU and plans were drawn up to establish the EMA, which did not open until five years later (1995). In 2000 the EMA introduced their Orphan Regulation and in 2001 the trials directive provided requirements for the conduct of trials in the EU.

#### 2.3.2.1 Orphan Drug Designation

The Orphan Drug Acts are the policies that have seen the most internationally widespread introduction and are the main tool aimed at overcoming the issues associated with rare disease drug innovation.

A 'rare' disease is defined as one which affects fewer than 5 people in every 10,000 in Europe (European Commission), and fewer than 200,000 people in the USA (Field and Boat, 2010, National Institutes of Health, 2013) (for comparison see Table 1).

Despite each disease affecting a small patient population, due to the large number, between 5-8,000 (Field and Boat, 2010), affecting up to 25 million people in the USA alone (National Institutes of Health, 2013), 'rare diseases' are a substantial policy concern.

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<sup>30</sup> <http://www.fda.gov/oc/ohrt/history.shtml>)

<sup>31</sup> <http://www.phrma.org/pdofa>

<sup>32</sup> <http://www.medscape.com/viewarticle/410910>

<sup>33</sup> The history of the EMA draws heavily on the 50<sup>th</sup> Anniversary brochure: [http://ec.europa.eu/health/human-use/50years/docs/50years\\_pharma\\_timeline\\_v2.pdf](http://ec.europa.eu/health/human-use/50years/docs/50years_pharma_timeline_v2.pdf) (accessed 24<sup>th</sup> April 2015)

Furthermore, with the increasing interest in ‘personalised medicine’ in general, involving the splitting of disease categories into smaller subtypes, using pharmacogenomics, it is possible that more diseases could be defined as ‘rare’, including cancer indications (Loughnot, 2005).

This molecularisation of cancer, i.e. the understanding of cancer in terms of the molecular pathways that contribute towards abnormal growth of tumour cells, permits the stratification of patient populations by tumour subtype (Hogarth et al., 2012). The process of splitting diseases in response to genetic and molecular understanding, has been discussed by Hedgecoe (2004). Furthermore, the alternative approach, ‘lumping’, has been implemented in rare diseases to rally public and political support. This happened early on in cancer, where Lasker and Farber in the middle of the 20<sup>th</sup> Century, encouraged the lumping of subtypes of cancer into larger groups, to motivate support (Mukherjee, 2011:155).

Region	Metric	Population (millions)	Comparable
EU	<5 in every 10,000	503	~251,500
USA	~6 in every 10,000	318.9	200,000

**Table 1 Comparable metrics for orphan drug designation in Europe and USA**  
**(Sources: [europa.eu/about-eu/facts-figures/living/index\\_en.htm](http://europa.eu/about-eu/facts-figures/living/index_en.htm) and [www.census.gov/popclock/](http://www.census.gov/popclock/))**

In addition to small patient populations and the associated market failure, the development of drugs for rare diseases also suffers from a lack of disease understanding, difficulty in diagnosis, difficulty in recruiting patients to trials, and issues with gaining statistical significance in trials (Field and Boat, 2010). In response to these, the US were the first country to introduce the Orphan Drug Act in 1983.

This was a culmination of 20 years of discussion and recognition, that drug development for rare diseases required incentives due to a lack of commercial viability. The main incentives offered by the Orphan Drug Act are 1) seven years market exclusivity, 2) availability of grants for product development, 3) tax credits for certain costs associated with trials, 4) FDA user fee waiver, and 5) advice to product developers on design of studies to meet regulatory standards (Field and Boat, 2010). This diversity of incentives is important because they represent both push and pull mechanisms (ibid).

With the USA paving the way, other countries introduced orphan drug policies, with Japan in 1993, Australia in 1997 and the European Union (EU) in 2000 (Field and Boat, 2010).

However, each country shows variations in the incentives offered (see Table 2). For instance, while Japan offer the longest period of market exclusivity, the policy does not imply an application fee waiver. In the EU some of the incentives offered to applicants in other countries are up to the discretion of member states.

<i>Incentive</i>	<i>United States</i>	<i>Japan</i>	<i>Australia</i>	<i>EU</i>
<b><i>Years of market exclusivity</i></b>	7	10	5	10
<b><i>Grants Programme</i></b>	Yes	Yes	No	Not at EU level <sup>34</sup> , member states' responsibility
<b><i>Tax credits for clinical research</i></b>	Yes (50% for clinical costs)	Yes (6% of clinical and non-clinical costs)	No	Not at EU level; member states' responsibility
<b><i>Assistance with trial design</i></b>	Yes	Yes	Yes	Yes (partial)
<b><i>Application fee waiver</i></b>	Yes	No	Yes	Reduced fees

**Table 2 Differences in countries' approaches to the incentives provided under Orphan Drug Acts (taken from Field and Boat, 2010: 30)**

The phase at which orphan status is gained varies between projects but is usually towards the later stages. For instance, in the dataset for this thesis of the six (out of a total of 11) projects that receive orphan drug status, half obtained it around the same time as approval, and the other half prior to phase III trials.

The Orphan Drug Acts have been successful in promoting the development of drugs for diseases affecting small populations. This is illustrated when comparing the decade prior to the US Orphan Drug Act (1983) in which only 34 “orphan drugs” received regulatory approval (3.4 per year), compared to 229 drugs entering the market (11.45 per year) in the twenty years that followed (Loughnot, 2005). By 2010, there had been 1,892 orphan designations (drug candidates) in the USA, with 326 approved products launched and marketed for more than 200 different diseases (Braun et al., 2010). In the EU, by 2011, there had been 850 orphan designated products, 60 (6 per year) of which received authorisation (Westermarck et al., 2011). Despite these figures indicating that the

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<sup>34</sup> The Innovative Medicines Initiative (IMI), which was launched in 2008, is directed at funding programmes in areas of unmet medical or social need (<http://www.imi.europa.eu/content/mission>). The IMI is, therefore, not focused specifically on orphan drugs but could be applied to some areas of rare disease drug development.

introduction of the Orphan Drug Act has been a success, there have been concerns over the unintended outcomes of the legislation.

The first of these concerns is the high prices demanded by the drug companies for approved orphan drug once they reach the market (Arno et al., 1995, Dear et al., 2006, Simon, 2006, Wellman-Labadie and Zhou, 2010). These high prices mean that marketed drugs may be inaccessible to some patients (Arno et al., 1995). In fact, some orphan drugs are even achieving blockbuster<sup>35</sup> status (Field and Boat, 2010). The high prices and inaccessibility of orphan drugs have been described as socially irresponsible (Hemphill, 2010) and unsustainable in the context of declining productivity in the pharma industry (Moors et al., 2014).

Another concern, following the introduction of the Orphan Drug Acts, is the exploitation of the legislation by industry. This has manifested in off-label use of orphan drugs, increasing the revenues obtained by the developing firm, paving the way for secondary, more broad indications to be investigated (Loughnot, 2005). These exploitation issues imply that the orphan drug legislation is being misused in disease areas other than those for which it is intended.

The final concern surrounding the implementation of orphan drug legislation is the safety and efficacy of these drugs, when compared to other approved drugs (Kesselheim et al., 2011, Dupont and Van Wilder, 2011). This stems from the difficulty in obtaining sufficient clinical data due to the tendency to enrol smaller patient numbers in trials for orphans drug and for these studies to be less commonly randomised and/or double blinded (Kesselheim et al., 2011, Dupont and Van Wilder, 2011).

#### 2.3.2.2 Accelerated Approval

Accelerated development and approval was introduced in 1992, as part of the Prescription Drug User Fee Act, to increase the speed of development and approval for drugs fulfilling unmet need (Borad and Von Hoff, 2008, Moore, 2003). Drugs qualify for accelerated approval when applied to a serious or life threatening disease, such as many types of cancer (Borad and Von Hoff, 2008). This regulatory policy is also of particular significance to cancer drugs because it allows the use surrogate endpoints<sup>36</sup> to indicate efficacy of the drug, rather than survival, or more direct endpoints (ibid).

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<sup>35</sup> Blockbuster status indicates sales of over \$1bn per year.

<sup>36</sup> Surrogate endpoints are used as indicators of efficacy in trials. In cancer, examples of surrogate end points are tumour shrinkage or biomarker levels, substituting for survival rates or improved



The endpoints used in accelerated approval must be ‘reasonably likely to predict clinical benefit’ and should be followed up by post-approval studies to garner further evidence about the associated risks (Borad and Von Hoff, 2008, Field and Boat, 2010). The use surrogate endpoints, however, has been highly controversial particularly in the area of cancer drug development, due to doubts about whether they are reliable indicators of the safety and efficacy of drugs (Davis and Abraham, 2011)

### 2.3.2.3 Fast Track

Fast track status was introduced by the FDA as part of the 1997 FDA Modernization Act (Reichert et al., 2008). Fast track status is applicable to drugs that aim to treat life threatening or severely debilitating illnesses that have the potential to address an area of unmet need (Moore, 2003, Borad and Von Hoff, 2008, Reichert et al., 2008). In drug development it is common for some interaction to exist between the FDA and the drug’s investigator during the review process (Lipsky and Sharp, 2001). However, fast track status can facilitate a higher levels of communication between stakeholders throughout development, in the form of frequent meetings, written correspondence concerning phase II and phase III planned trials, as requested (Moore, 2003). Furthermore, fast track status can decrease the time taken to review a drug application for approval, from 10 months to 6 months (Borad and Von Hoff, 2008).

Despite being a useful regulatory policy tool, particularly for small biotech firms who may have less experience in developing drugs and getting through approval stages, the Fast Track policy has been criticised for its apparent lack of transparency (Reichert et al., 2008). Despite these issues, the policy does show value in bringing otherwise difficult to develop drugs to the patient populations most in need (ibid).

### 2.3.2.4 Compassionate Use/Expanded Access

In addition to regulatory policies encouraging innovation for rare cancers and serious/life threatening diseases presenting unmet clinical need, compassionate use/expanded access is also a strategy used to aid innovation, particularly, in cancer drug development.

Compassionate use, or early or expanded access to promising drugs, introduced under the Special Protocol Exception at the FDA, allows patients access to drugs prior to regulatory approval (Moore, 2003). Expanded access to cancer drugs is associated with

increasing numbers and action of patient advocacy groups in recent decades<sup>37</sup>. Despite the introduction of the Investigational New Drug Treatment Program legislation by the FDA in 1987, as part of the FDA Modernization Act, the history of cancer patients gaining expanded access to treatments really began with the development of Herceptin (trastuzumab) (see Chapter 5) (Baldwin, 2002). When Herceptin showed promising results in trials patients began to put pressure on the developing company, Genentech, in order to gain access to the drug (Bazell, 1998, Baldwin, 2002).

Despite the apparent public support for such expanded access programmes, there are clearly potential issues with safety when providing expanded access to a drug prior to it having gone through proper trials and regulatory approval (Baldwin, 2002, Genève, 2003). Furthermore, while programmes such as these involved substantial cost to the organisations involved, this is balanced by the benefits to the organisation in patient recruitment to trials and publicity (Baldwin, 2002).

#### 2.3.2.5 Critical Path Initiative

In 2004 the FDA published a White paper, *Innovation and Stagnation*, investigating the so-called *Pipeline problem*, of the aforementioned productivity crisis (FDA, 2004). In this paper the FDA highlighted a discrepancy between the advances that had been made in the discovery of new drug, due to the developments in the associated basic science, and the applied science necessary to match this advancement in development phases (FDA, 2004). This paper stimulated much debate surrounding the previously unrecognised lack of scientific approaches in drug development, in response the Critical Path Initiative was introduced by the FDA in 2006 (Woodcock and Woosley, 2008).

This initiative aimed at improving the drug development process and balancing the tensions between ensuring product safety, while also encouraging the production of innovative drugs, in light of the increasing realisation of the productivity crisis (ibid). Calling for the development of 'a new product development toolkit', encompassing animal or computer-based predictive models and new clinical evaluation techniques, the FDA set out to influence this through the standards implemented to guide development programmes (FDA, 2004). The implementation of the Critical Path Initiative led to the perceived improvement of the scientific approach to drug development processes,

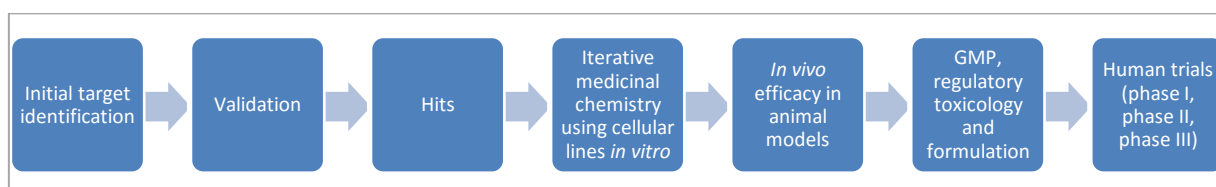
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<sup>37</sup> The role of patient groups is further explored in Chapter 3, section 3.3.1.

including in clinical trial methodologies, the production and utilisation of biomarkers and the application of bioinformatics (ibid).

### 2.3.3 Clinical Trials – Standardisation, Costs, Attrition

The standardisation of clinical trials, as will be explored in this section, is relevant in this Chapter for two reasons. Firstly, because it provided a platform for the regulatory approval of drugs, and secondly, due to the facilitation of accumulated knowledge of a drug, its mechanism of action and interactions in the body. Furthermore, this section highlights the substantial difficulty, in duration, cost and attrition rates of clinical trials, facing drug developers. Clinical trials are carried out once a drug is deemed to show sufficient safety *in vitro*<sup>38</sup> and in animal models (referred to as preclinical trials) (summarised in Figure 1).



**Figure 1 Process leading up to first-in-man trials (taken from description in (Kelland, 2008))**

During the period 1950 to 1970 leukaemic cell lines were predominantly used in preclinical testing, however by the late 1970s/early 1980s human tumours transplanted onto animal models became more commonplace (DeVita and Chu, 2008, Kelland, 2008). More recently screening is being undertaken with reference to specific molecular targets, rather than generic panel screening (DeVita and Chu, 2008).

Once safety and efficacy have been proved sufficiently in preclinical studies, trials in human subjects can begin. This generally involves phase I, phase II, phase III and phase IV (post-marketing) trials. Despite this apparent division into distinct phases, it has been observed that in practice the barriers between these stages are blurred (Borad and Von Hoff, 2008). It remains useful, however to outline the clinical phases as distinct stages as it is a useful tool to picture the whole process.

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<sup>38</sup> *In vitro* studies are carried out on cells under controlled experimental conditions that are outside the cell's natural environment, for instance, a test tube. This is contrast to studies *in vivo* in which organisms are tested as a whole, for instance, testing in animals.

Initial phase I trials typically involve around 100 healthy subjects (costing between \$200,000 and \$800,000 (Hill, 2012:241)), before moving on to testing the drug in a small number of the target patient population (Neal, 2012). The purpose of these primary human trials is to assess the pharmacokinetic and pharmacodynamic profile of the drug (ibid). Pharmacokinetics is the study of 'drug absorption, distribution, metabolism and excretion', i.e. how does the drug interact with, and get eliminated from, the body (Ratain and Plunkett, 2003). Pharmacodynamics is the study of the relationship between dosage of the drug and patient response (ibid).

Phase I studies should illustrate the safety and tolerability of a molecule, and ideally giving an indication of efficacy (Field and Boat, 2010, Neal, 2012). In cancer trials it is often the case that phase I will involve people with a broad range of cancer types, if the specificity of the drug has not been ascertained in preclinical investigations.

Phase II trials tend to involve a larger number (between 250 and 700 patients, (Hill, 2012:241)) of patients suffering from the specific indication(s)<sup>39</sup> for which the drug is being developed, representing a significant step in the development process (Neal, 2012). These trials typically costs between \$2.5m and \$6m+ (Hill, 2012:241). There are three main objectives of phase II trials: 1) to provide evidence that the drug is efficacious (i.e. it works at treating the disease it is aimed at), 2) to establish a balance between the minimum dose to achieve effectiveness and the maximum dose that can be tolerated by patients, and 3) to determine a safety profile of the product (Field and Boat, 2010, Neal, 2012).

Phase III is usually the 'pivotal', or confirmatory, phase, i.e. the final stage before a drug can be presented for regulatory approval. Typically the aim of this stage is to provide statistically significant data that the drug is efficacious (i.e. more effective than a placebo or standard therapy) and safe (preferably safer than a comparator, marketed drug) (Neal, 2012). Typically larger than phase II (involving 500-1000 patients and costing between \$2-\$10m (Hill, 2012:241)), phase III trials almost always take place across a range of international study centres and usually take between one and four years to complete (Neal, 2012). Post-marketing surveillance studies are carried out post-approval and therefore are not relevant to the research presented in this thesis.

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<sup>39</sup> An 'indication' is defined as the specific disease for which the drug is being developed. A primary indication is the lead indication for development, where additional indications being investigated are termed secondary indications.

Development times have increased over the past 20 years, whereby the average duration of clinical development, from patent to commercialisation has gone from 9.7 years in the 1990s to 13.9 years in the 2000s (Pammolli et al., 2011). Furthermore, the duration of trials also shows a high level of variation (on average between 6 and 8 years) (Pammolli et al., 2011) between different indications, by type of product and dependent on the type of organisation responsible for development (Abrantes-Metz et al., 2004). The increase in the duration of trials has been associated with the rising tendency, in the industry, to pursue high risk, chronic diseases (Pammolli et al., 2011).

The use of different approaches to drug innovation has influenced the variation in durations of clinical trials. For instance, between the years 1989-2002, successful phase I trials were found to last, on average, 19.7 months, ranging from 18.76 months for non-big pharma to 19.62 months for big pharma. To successfully complete phase II trials took on average 29.87 months (29.92 for non-big pharma, 25.11 for big pharma) and successfully completing phase III took on average 47 months (49.07 for non-big pharma and 41.43 months for big pharma) (Abrantes-Metz et al., 2004). When measured, biologicals took the least time to successfully complete phase I (17.87 months), with natural products taking the most time to reach the same milestone (21.5 months). In phase II trials this pattern switches, where biologicals take the longest duration to successful completion, at 31.87 months vs. 19.44 months for natural products. In phase III, however, chemicals take the longest duration to successfully complete (at 47.74 months, with natural products at 46.14 months, and biologicals at 45.63 months) (ibid).

For anti-cancer drugs, successfully completing phase I trials was the longest duration of any other indication sub-group (21.79 months vs. an average of 19.68 months), however, anti-cancer drugs took relatively less time to successfully complete phase II trials. To successfully complete phase III trials anti-cancer drugs took 47.75 months, just over the average for the whole dataset at 47 months (Abrantes-Metz et al., 2004). Overall clinical development times for cancer drugs have been found to be comparatively longer than other indications (by 1.5 years in the US), although approval times were shorter for oncology projects on average (0.5 years) (DiMasi and Grabowski, 2007). This data has, so far explored successfully completed trial phases, perhaps unsurprisingly 'failed' (where the project was withdrawn by the developing company, or the FDA rejects the project) trials take considerably longer (Abrantes-Metz et al., 2004).

Trials are an expensive undertaking, lengthy and show high failure (attrition) rates. In cancer drug trials from 1990-2000 the rate of failure was less than half that of drugs for other diseases (Kola and Landis, 2004, Workman and Collins, 2008). However, oncology

drugs disproportionately receive support from the FDA in the form of priority review, orphan drug and fast track status and are therefore achieve similar approval rates when compared to drugs for other diseases (DiMasi and Grabowski, 2007, Workman and Collins, 2008). This indicates that drugs produced for cancer generally tend to benefit from a faster review process by the FDA, increased periods of market exclusivity and input from the regulatory body throughout the drug's development.

There is a direct link between the time taken to complete trials sufficiently to obtain regulatory approval, and the subsequent overall costs of drug development. It is expected, therefore, that oncology drugs, due to their longer development times, would be more expensive than the average drug project to get to the market. Estimates of drug development costs are between \$650-1,023m (DiMasi et al., 2003)<sup>40</sup>, with oncology drugs being represented at the higher end of this range.

As discussed, as a drug progresses through trials, costs increase. Furthermore, for each day of delay the organisation is losing a huge amount of money in lost potential sales, for instance, around \$2.75m in the case of a blockbuster (sales of \$1bn per year). Reasons for failures change over time. 1990s failures stemmed from poor predictions of patient-drug interactions, and, more recently (2000s), lack of efficacy and intolerable levels of toxicity are the limiting factors (Kola and Landis, 2004, Workman and Collins, 2008).

One strategy implemented to attempt to reduce failure rates, and therefore costs of drug development of cancer drugs is the stratification of patient populations, by either demographics (i.e. patients over or under a certain age) or the molecular action of the drug (Borad and Von Hoff, 2008). Here, the study of pharmacogenomics has been central to the development of cancer therapeutics, whereby a genomic information is

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<sup>40</sup> Despite the DiMasi et al (2003) figures being the most highly cited, estimations of the costs of developing a drug are highly contentious. For instance, Light and Warburton (2011) critique DiMasi et al. (2003) and claim that their figures are overestimated for the following reasons: 1) only drugs developed and originated in-house are included, where in-licensed drugs are estimated to be four times cheaper), 2) no data is presented on estimations of failure rates which are used to inflate figures to account for expenditure on unsuccessful drugs, 3) R&D tax subsidies are not accounted for, 4) variations between different firms and therapeutic categories are not taken into account, 5) cost of capital (i.e. money that was lost from not making investments for the duration of the R&D expenditure) is estimated to be 11% accounting for doubling the cost estimate (from \$403m to \$802m), 6) inflation rates take the estimate of \$802m in 2000 US dollars to \$1.32bn in 2006 and an estimated \$2.16bn in 2012, and 7) R&D costs used for estimate are volunteered from firms with no information presented as to which firms have been used or how R&D costs are being calculated.

taken to inform the diagnosis, treatment and study of their disease (Webster et al., 2004, Hopkins et al., 2006).

By targeting a specific abnormality and recruiting relevant patients to trials there is a higher chance that patients will be responsive to the treatment, and therefore efficacy levels are higher (Heemstra et al., 2011). Furthermore, in focusing development on particular molecular cancer subtypes, clinical development does not rely on previous comparators and can therefore sometimes be cheaper and more straightforward. This strategy may also help to decrease the toxicity levels of cancer drugs due to their specificity to cancer cells rather than any proliferating cells in the body.

#### **2.3.4 Industry dynamics**

In addition to shifts in the scientific approaches, policy, regulatory and funding environments for drug development and cancer therapeutics, instigated by the 'war on cancer', the dynamics of the industry surrounding drug development also changed post-1970. With an increasingly rational approach to drug discovery, where firms can strategically focus on particular diseases, there has been a shift from acute (e.g. infections), to chronic diseases (such as cancer) (Hopkins et al., 2007, Martin et al., 2009).

In the pre-1970 period drug development was denominated by academic research labs and large chemical companies, with substantial cancer research support coming from the public purse and charitable sector. However, the change in the use of molecular biology led to an influx of new companies focusing on biological understanding of, and developing therapeutic treatments for diseases (Achilladelis, 1999, Nightingale, 2000). The introduction of new technologies, including biotechnology, had effects on the industry both strategically and structurally.

Despite the high expectations around the promise of biotechnologies, the period since the 1970s has seen a declining productivity in the industry and pharma pipelines dwindling (Nightingale and Martin, 2004, Hopkins et al., 2007, Pammolli et al., 2011, Martin et al., 2009). There are several reasons that have been put forward to explain this trend: 1) increased complexity and shifting bottlenecks (Nightingale and Martin, 2004, Hopkins et al., 2007), 2) increasing interest in high risk areas, therefore higher probability of failure (Pammolli et al., 2011) (Martin et al., 2009), 3) increased attrition rates, therefore increased costs (Hopkins et al., 2007, Pammolli et al., 2011), 4) increased competition in the marketplace (Pammolli et al., 2011), 5) more existing therapies available, therefore higher thresholds for new drugs in these areas (Scannell et al., 2012),

6) easy targets/low hanging fruit have been explored (Pammolli et al., 2011, Hopkins et al., 2007), 7) the 'cautious regulator' problem (Scannell et al., 2012), 8) the 'throw money at it' tendency (Scannell et al., 2012), and 10) the tendency to rely, too heavily on advances in basic research and screening methods (Scannell et al., 2012).

However, in oncology, the development of targeted therapies has had a positive effect on attrition rates. In general cancer drugs show an 82% attrition rate (akin to failure rate), in contrast to the that for kinase inhibitors (one of the largest types of targeted therapy) which was 53% (Walker and Newell, 2009). Furthermore these targeted therapies were found to be more successful in transitioning from phase II to phase III, indicating the potential to reduce costs.

Despite the benefits for cancer patients of more oncology appearing in pharma pipelines, and the shift to targeted therapies, which were predicted to be more efficacious and less toxic, these trends also contribute towards an increasingly competitive market (Stewart and Naeymi-Rad, 2011). This will not only lead to declining market shares for firms, but also competition for patients in trials, thereby implying lengthier durations, higher costs and potential patent issues (ibid).

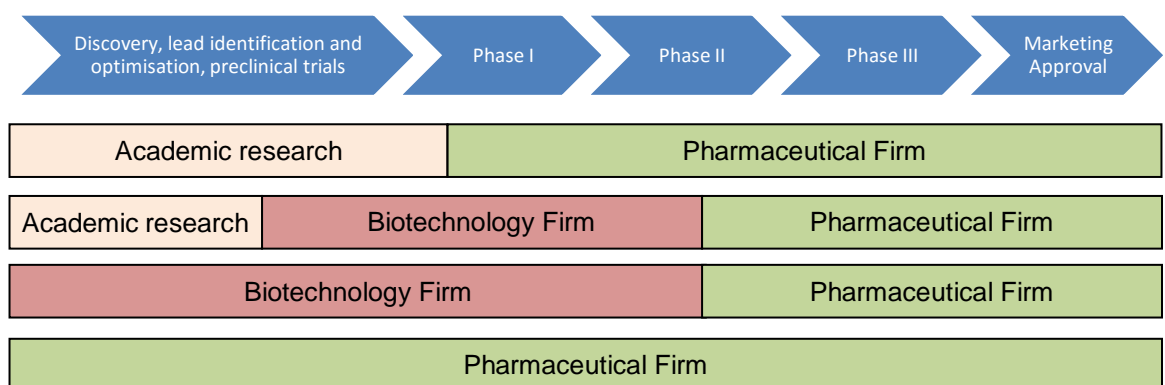
Structurally with the advent of molecular biology and the increased use of biological processes in drug discovery and development the industry has seen an influx of smaller organisations emerged. This stemmed from the realisation of the potential of these new technologies, by academic molecular biologists and venture capitalists (Pisano, 2006:84-85, Hopkins et al., 2007). However, with the substantial costs associated with late stage drug development, and the need to realise economies of scale and scope through experience, capabilities and networks, small firms were generally not able to compete with incumbent pharma (Scriabine, 1999b, Cockburn and Henderson, 1999). Therefore, emerging companies tended to be small and specialised (Malerba and Orsenigo, 2002).

However, early on in the introduction of new molecular approaches the incumbent pharmaceutical firms, who were previously responsible for producing drugs, stayed away, adopting a 'wait and see approach' (Hopkins et al., 2007). This allowed some early mover new biotech firms to grow into fully integrated pharmaceutical companies (Pisano, 2006-85), as was the model demonstrated by big pharma, e.g. Genentech and Amgen. However, at least initially, these firms were reliant on collaborations with other companies to gain access to the skills they lacked (Pisano, 2006). Since then increasing interest and investment from big pharma into biotechnology (Martin et al., 2009), for instance in mabs (Hopkins et al., 2007), has led to the development of in-house capabilities and led to a rise in external collaborations.



For big pharma collaborations provide access to knowledge and capabilities from small firms, for instance, focusing on specific diseases, reliance on platform technologies for internal R&D projects or providing services (Pisano, 2006:84-85). Significantly, small firms with genomics capabilities began initially (in the 1970s) by providing contract research services generating knowledge about drug-target interactions to guide screening (Martin et al., 2009). However, in the 1990s where biotech moved away from contract research work, towards functional genomics (i.e. furthering the understanding of genes and the proteins they coded) and development of technologies (ibid).

When pharma realised the importance of new technologies, profitable and mutually beneficial collaborations between smaller, newer biotech firms and older, larger incumbent firm were established. Here, pharma could gain access to specialist expertise and new technologies, and biotech could fill the gap in commercialisation and marketing capabilities, skills and resources (Malerba and Orsenigo, 2002, della Valle and Gambardella, 1993, Galambos and Sturchio, 1998).



**Figure 2 Simplified representation of the organisations typically responsible for the drug discovery and development pathways**

The dynamics of collaborations, between of biotech firms, universities/research institutes and pharma have been a key part of the industry over the past 40 years. In 1996 Powell examined the inter-organisational relationships and commented that ‘no single firm has all the necessary capabilities’ and therefore membership of a networks of collaborations is necessary (Powell, 1996a).

In response to these trends, since the 1970s drug development has been dependent on a network of collaborative agreements involving public organisations, and funding, as well as private companies, both large and small (della Valle and Gambardella, 1993, Malerba and Orsenigo, 2002). This has led to a restructuring of the industry whereby

networks of organisations and agreements between organisations become the main governance structure (Staropoli, 1998, Powell, 1996b). These relationships can also be conceptualised as being cyclical: new technologies initially promoted the establishment of new firms, which, thanks to the associated hype, led to an increase in investment into the industry, in turn permitting the development of novel technologies and business models and further division of labour.

The emergence of networks of collaborative relationships have led to a distributed and open R&D process characterised by the proliferation of research trajectories and based on division of labour and new forms of organisational and industry dynamics (Orsenigo et al., 2001, Malerba and Orsenigo, 2002).

It follows that biotech firms are indispensable to the industry, particularly in the context of declining productivity of pharmaceutical companies. This is demonstrated in an analysis of 252 new drugs approved between the years 1998 and 2007, Kneller found that around half of the scientifically innovative drugs, and half of those aimed at unmet medical needs, originated in biotech (Kneller, 2010).

It is therefore worrisome that biotech suffers from vulnerabilities in industrial dynamics, stemming from inexperience, but most commonly from a lack availability of funding. Biotechnology firms receive funding from a complex web of actors including, high net worth individuals, government grants, charities and universities at the early stages, and venture capital, stock markets and business angels at the mid and late stages. Small firm funding conditions have oscillated throughout the past 30 years.

Traditionally stock-markets and VC were the main funding source for biotech to gain access to sufficient funding to develop projects past phase II trials (Hopkins et al., 2013). However, in the wake of high profile failures these funding sources closed in the late 1990s, proving fatal to some in the industry with the early 2000s characterised as a period of financial difficulty for small firms (Martin et al., 2009). Furthermore, funding sources can be unpredictable and often do not allow small firms access to cash when needed, leading to, in some cases, M&A based on desperation (Hopkins et al., 2013).

Typically companies either become sustainable in generating revenue (through offering services or technology platforms to other companies, licensing agreements or generating royalty revenues from previous projects) or are sold as part of a merger or acquisition (Hopkins, 2012).

This section has demonstrated shifts in the industrial environment surrounding drug development for cancer. Here the post-1970 period has witness a rise in a new business

model, in the advent of biotech firms, in response to the development of new molecular technologies, and a change in the strategic direction of firms that have, in some instance led to a crisis of productivity. We will now turn to the development of cancer drugs, in particular, and the research trajectories contributing towards the shift to targeted therapeutics.

### **2.3.5 Cancer Research post-1970**

One of the early streams of cancer research was undertaken by Michael Bishop and Harold Varmus who, at the University of California, San Francisco (UCSF) in 1970 began work that led to the concept of oncogenes and proto-oncogenes (Bazell, 1998). Bishop and Varmus were studying chicken viruses in an attempt to identify how normal cells could become cancerous (*ibid*). The link between viruses and cancer was thought to stem from the ability of some viruses to penetrate cells, and initiate replication, thereby promoting cell proliferation (*ibid*).

Bishop and Varmus's work identified a gene in human cells, usually found in virus DNA that could initiate this behaviour causing cancer. This led to the coining of the term 'oncogene', to imply a gene that causes abnormal replication of a cell (Bazell, 1998). In 1976 Varmus and Bishop published an article that concluded that oncogenes were normal genes (proto-oncogenes) that mutated to become abnormal (Stehelin et al., 1976, Bishop, 1982).

Oncogenes are now defined as 'genes that cause normal cells to grow out of control and become cancer cells... they are formed by the mutations of certain normal genes of the cell called proto-oncogenes' (Sudhakar, 2009). Conversely genes that are normally responsible for controlling cell division, DNA repair and cell death but when malfunctioning allow cells to divide out of control, are termed tumour suppressor genes (Sudhakar, 2009).

The research by Varmus and Bishop in the 1970s was built upon in the early 1980s by Axel Ullrich who initially worked at the UCSF with Bishop and Varmus but later went to Genentech, one of the first biotech firms (Bazell, 1998). In 1983 Ullrich worked with a British protein chemist, Michael Waterfield to garner evidence of the process by which oncogenes could cause cancer (Bazell, 1998). This culminated in an article stating that one particular oncogene, *erb-b*, was a mutated form of the epithelial growth factor (EGF) (Ullrich et al., 1984). This discovery was significant because it verified the link between research surrounding cell growth signals and cancer (Bazell, 1998).

This research led to the US Special Virus Cancer Program, initiated with the purpose of identifying viruses associated with cancer (DeVita and Chu, 2008). The programme was not particularly successful in this, and was therefore renamed the Program of Molecular Biology, with the altered aim of identifying oncogenes (ibid). However, viruses and their link with cancer continue to be a relevant stream of research (e.g. with Human papillomavirus).

The Program of Molecular Biology led to a deeper understanding of the genetic basis for cancer abnormalities, providing an array of targets which could be used to design drug compounds. This proliferation of targets has recently been described as representing a shift from a lack of cancer drug targets to an excess (Workman and Collins, 2008). Such targets now include: activated oncogenes, inactivated tumour suppressor genes, genes leading to DNA repair defects, genes supporting oncogenic pathways, and genes controlling the tumour microenvironment (Workman and Collins, 2008).

The past 40 years of cancer research has widely been described as a new era for oncology. This shift in the way that knowledge around oncology has been constructed also manifests in the transition from simple cytotoxins with relatively low selectivity to cancerous cells, to targeted therapies with higher levels of specificity (DeVita and Chu, 2008). The reliance on knowledge of the molecular makeup of tumours, in theory, leads to less toxic and more efficacious treatments.

The development of cancer therapeutics has seen a shift in operational principles, from cytotoxic approaches to targeted therapeutics. Broadly speaking approaches to developing drugs in this area have based on the strategies of cancer cells to grow and divide. These have been summarised into six acquired capabilities of tumour cells: 1) insensitivity to anti-growth signals, 2) self-sufficiency in growth signals, 3) evading apoptosis, 4) limitless replicative potential, 5) sustained angiogenesis (blood vessel formation) and 6) tissue invasion and metastasis (Hanahan and Weinberg, 2000). The following sections provide a scientific and technological knowledge foundation behind the novel cancer drug families directly relevant to the case histories in this thesis: kinase inhibitors, mabs, and immunotoxins.

#### 2.3.5.1 Kinase Inhibitors

Protein kinases are proteins that provide a good target for anti-cancers due to their integral role in signalling pathways that regulate cellular functions, such as DNA replication, cell growth, proliferation and differentiation (Grant, 2009). Protein kinases act by catalysing the process of protein phosphorylation facilitating signalling mechanisms

(ibid). The link between phosphorylation and cellular functions was first published in 1966 (Fischer and Krebs, 1966) and, combined with the discovery that some protein kinases can act as oncogenes in 1976 (Stehelin et al., 1976), led to the recognition of the potential for protein kinase inhibitors to be used as anti-cancer agents (Grant, 2009).

By 2009 there had been over 30 kinase drug targets identified, representing a huge interest in kinase inhibitors as an avenue for cancer treatment (Zhang et al., 2009). These drug targets fit in four broad categories of kinases: receptor tyrosine kinases, cytoplasmic tyrosine kinase, serine/threonine kinase and lipid kinase (Zhang et al., 2009).

Kinase inhibitors can be targeted with either mabs (see Section 5.4.3.5) (e.g. bevacizumab (Avastin) targeting the vascular endothelial growth factor receptor (VEGFR) and, trastuzumab (Herceptin) targeting the HER2 receptor) or small molecule inhibitors (e.g. pazopanib (Votrient) targeting the VEGFR receptor, and imatinib (Gleevec) targeting the BCR-ABL, c-Kit and PDGFR receptors) (Gerber, 2008).

The projects in this thesis that can be categorised under the umbrella of kinase inhibitors are: pazopanib (a tyrosine kinase inhibitor) and barasertib (an aurora kinase inhibitor).

#### 2.3.5.1.1 *Tyrosine kinase inhibitors*

The tyrosine kinases make up two of the four kinase categories (the receptor and cytoplasmic tyrosine kinases), representing 18 of the aforementioned 30 known kinase drug targets (Zhang et al., 2009). Tyrosine kinases are proteins responsible for signalling between cells mediating activities such as cell proliferation and migration (Gotink and Verheul, 2010). For the purposes of this thesis we are most interested in the vascular endothelial growth factor receptor (VEGFR) as this is the relevant target for pazopanib (Chapter 6).

VEGFR is a receptor tyrosine kinase involved in angiogenesis (Gotink and Verheul, 2010). Receptor tyrosine kinases, such as VEGFR, act on extracellular signals into the cell, while non-receptor tyrosine kinase inhibitors act on intracellular communication (Gotink and Verheul, 2010). Specifically VEGFR acts as a proangiogenic factor, promoting the development of blood vessels around the body (Eskens and Verweij, 2006). By inhibiting VEGFR drugs such as pazopanib (see Chapter 7) act to arrest angiogenesis in tumours, hence starving cells of a blood supply, leading to cell death.

Angiogenesis was first described to be a crucial process in tumour development, and therefore recognised to be a potential target for anti-cancers, in 1971 by Judah Folkman (Folkman, 1971). However, the discovery of the tumour-derived blood vessel growth

stimulating factor dates back to 1939 (Ide et al., 1939). It has been observed that in the intervening time (from 1939 onwards) ‘independent and unrelated lines of research converged toward to identification of VEGF’ (Ferrara, 2002). This stream of knowledge was brought together when the term VEGF was coined in 1989 (Ferrara and Henzel, 1989).

#### 2.3.5.1.2 *Aurora kinase inhibitors*

As a subtype of kinase inhibitors aurora kinases are a relatively recent development in the area of cancer therapeutics. The aurora kinase targets were first identified in 1995 in fruit flies where they were found to be required for cell division<sup>41</sup> (Francisco et al., 1994, Glover et al., 1995). Just three years following this discovery research published by scientists from SUGEN, a biopharmaceutical company based in the USA, in collaboration with UCLA School of Medicine (Division of Hematology-Oncology and Jonsson Comprehensive Cancer Center) and University of Texas (Department of Microbiology) discovered a human form of the aurora kinases (at the time termed *aurora 1* and *aurora 2*, now referred to as Aurora A and B) were overexpressed in human cancer cells (Bischoff et al., 1998).

Aurora kinases are known to be involved in regulating the process of mitosis, where cells divide to grow (Keen and Taylor, 2004, Coumar et al., 2009). The anti-tumour effect of aurora kinase inhibitors was thought to come from the idea that if mitosis is interrupted, cells cannot longer divide and grow and therefore tumours cannot develop. Since the initial discovery of the activity of human aurora kinases, aurora A, B, and C have been suggested as potential drug targets for anti-cancer therapeutics (Coumar et al., 2009)

#### 2.3.5.2 Monoclonal Antibodies (mabs)

The work contributing to the development of mabs can be traced to the research by Cesar Milstein and Georges Kohler at the Laboratory of Molecular Biology at the Cambridge University (Hale and Waldmann, 2000, Clark, 2005, Marks, 2015). In 1975 the first monoclonal antibody (mab) was generated in mice using the hybridoma technique (Kohler and Milstein, 1975, Liu, 2014).

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<sup>41</sup> There are two types of cell division: 1) mitosis occurs when two daughter cells are formed that are identical to the parent cells, and occurs in most dividing cells around the body, 2) meiosis occurs when daughter cells contain half the genetic material of the parent cells, and occurs in the sex organs to produce reproductive cells (gametes).

Milstein's interest initially lay in determining the diversity of antibodies, the naturally occurring proteins responsible for fighting foreign bodies (Marks, 2013b, Marks, 2015). By building on the discovery that myeloma cells produced just one type of antibody rather than the diverse array found in normal tissue (discovery by Kunkel, an American immunologist based at the Rockefeller Institute, New York in 1951), and advances in technologies surrounding the ability to produce myeloma cells, Milstein and Kohler's research team began to discover ways to produce antibodies with known specificity to particular target antigens<sup>42</sup> (Marks, 2013b, Marks, 2015). In order to do this Milstein and Kohler found that by fusing a normal B cell from the spleen of a mouse, immunised with a specific antigen, with a myeloma cell, they could produce a hybrid cell that could secrete antibodies of known specificity, and survive indefinitely (Marks, 2013b, Marks, 2015, Liu, 2014). This technology would later be dubbed hybridoma technology, and described as a method to produce mabs.

Controversially, this UK technology was not patented, with the National Research Development Corporation (the public body responsible for the commercialisation of academic discoveries at the time) concluding that they could not 'identify any immediate applications' (Marks, 2013b). With the subsequent publication of the Spinks<sup>43</sup> committee report, the new conservative government at the time, led by Thatcher, and the realisation of the potential applications of biotechnology, the decision not to patent was hailed as a repeat of the mistakes made in the missed commercial opportunity surrounding penicillin (Tansey and Catterall, 1997).

These mistakes were, however, not immediately apparent due to the lack of success of early attempts at using mabs as therapeutics. This lack of success came from the difficulty of using animal cell lines in the production of antibodies, causing immunogenicity (ability to induce an immune response in the body) (Liu, 2014, Nelson et al., 2010). Humanisation is required to overcome this. The most popular strategy used for reducing the murine component of mabs was in the combination of rodent and human sequences, producing humanised or chimeric mabs (Nelson et al., 2010).

This new approach to mabs has enabled it to become a popular strategy for drug discovery, particularly in oncology, that has reaped substantial success, with six out of

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<sup>42</sup> Antigens are the substances that initiate an immune response in the body, for instance, chemicals, bacteria, viruses or pollen ([www.nlm.nih.gov/medlineplus/ency/article/002224.htm](http://www.nlm.nih.gov/medlineplus/ency/article/002224.htm))

<sup>43</sup> The Spinks report, published in 1980, was the first effort to produce a coherent policy for biotechnology in the UK.

the ten best selling drugs being antibodies (Marks, 2013b, Marks, 2015), and peak sales predicted to reach \$50 billion in 2012 (Morrow, 2012). In the dataset for this thesis several cases discussed were derived from antibody technology.

#### 2.3.5.3 Immunotoxins/Antibody-Drug Conjugates

Immunotoxins and antibody-drug conjugates have been grouped together here because they are both the product of the conjugation of two components, one responsible for targeting the cell, and the other a drug or toxin. Here the antibody activates the drug/toxin conjugate upon binding to the cell receptor leading to cell death. Antibody-drug conjugates involve the combination of an antibody with a drug, usually a known anticancer drug, and immunotoxins are made up of an antibody-toxin conjugate (Teicher and Chari, 2011). Of the cases used in this thesis, gemtuzumab is classified as an antibody-drug conjugate, and CAT3888 and TransMID are both immunotoxins (see Chapter 7).

The area of research contributing towards antibody conjugates and immunotoxins dates back to the 1950s with the idea that antibodies could be used to target tumours (Pressman and Korngold, 1953). The concept of immunotoxins can be traced to the work of Albert on prodrugs which suggested that drugs can be activated *in vivo* to produce a therapeutic effect (Albert, 1958, Singh et al., 2008). This is applicable to immunotoxins as these involve a cell receptor binding molecule, in this case an antibody that activates a drug/toxin conjugate upon binding to the cell receptor leading to cell death, producing a targeted response.

Immunotoxins and antibody-drug conjugates arose out of the realisation that few antibodies have the ability to kill cells in sufficient numbers to induce a significant tumour response (Pastan, 2003). Antibody conjugates (both antibody-drug conjugates and immunotoxins) represented a new wave of cancer therapeutics in the 1980s where many scientists were exploring different combinations of toxins (and drugs) and antibodies (Pastan, 2003).

Initially, in the 1970s, investigators at Ira Pastan's NCI lab focused on developing an understanding of the process of absorption of growth factors, hormones and viruses, into cells (ibid). In 1983, the team realised the potential of targeting a particular toxin, *Pseudomonas exotoxin*, to cancer cells using antibodies as a mechanism of targeting (Fitzgerald et al., 1983). In addition to *Pseudomonas exotoxin*, other toxins used in early research of immunotoxins were diphtheria, pokeweed anti-viral protein, ricin, abrin and gelonin (Teicher and Chari, 2011). As with mabs, the main limitation to the testing of initial efforts in immunotoxins, was the immunogenicity of the antibodies used and the



difficulties associated with the large size of the antibody component causing issues with penetration into solid tumours (Teicher and Chari, 2011). This realisation led to a second generation of immunotoxins using antibody fragments produced through recombinant techniques (Teicher and Chari, 2011). The strategy of antibody-drug conjugate approach utilised anticancer drugs adjoined to mabs in order to improve their selectivity and therefore therapeutic index (Teicher and Chari, 2011)

## **2.4 Conclusion**

This Chapter has provided the necessary contextual basis for an assessment of the data that will follow in the subsequent Chapters, 6 and 7. The first, pre-1970 section highlighted the establishment of policies, industry, regulatory systems, institutions and funding which provided a solid foundation for drug discovery and development through trial and error investigations. Furthermore, we also demonstrated how these developments had particularly positive consequences for the development of cancer therapeutics. This involved an increasing awareness during the mid-20<sup>th</sup> Century in the US and UK, from policy, the public, and scientists, for the need for a centralised effort to combat cancer.

The second half of the Chapter explored the implications of these advances in the post-1970s period, where scientific understanding and new technologies led to the coevolution of regulatory processes, drug discovery and development approaches, and industry structure and strategy. These shifts, in the increasing reliance on a molecular understanding of disease for drug discovery and development, and industrial dynamics, represent trajectory shifts constrained by environmental selection pressures. These constraints have led to doubt of the impact these developments have had in terms of benefit to patients<sup>44</sup>.

In these discussions we have witnessed the increasing interest in cancer research, from the public, policy-makers and industry. In the time before Nixon's declaration of the War on Cancer, oncology was perceived to be akin to quack medicine. This is in stark contrast to present day NIH budget metrics which place cancer as the highest funded disease area<sup>45</sup>. This trend has coevolved with the shift in drug development more broadly,

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<sup>44</sup> This disappointment is related to both the difficulties in adapting to changing technological trajectories and the influence of path dependency, as well as the high costs and low levels of Quality Adjusted Life Years that have been associated with newly developed treatments.

<sup>45</sup> [http://report.nih.gov/categorical\\_spending.aspx](http://report.nih.gov/categorical_spending.aspx)

involving new approaches and technologies modalities, and the resultant shift in the industry and regulatory environment.

This thesis aims to explore the selection pressures acting on these shifts and the direct influence they have on the development of drug innovations. This Chapter has facilitated an appreciation of the diversity of organisations and increasing complexity in this process. Due to the complex interactions between organisations involved in biomedical innovation there is an emphasis on knowledge, resources and knowledge transfer, and the multiplicity of the organisations, individuals and stakeholders involved in this process, facets of which are discussed in Chapter 3.

In the following Chapter we will also explore the literature surrounding biomedical innovations and thereby formulate a framework to guide the research design. This literature review will also justify the focus on drug projects, due to the frequency of studies that take the organisational drug, i.e. the locus of innovation, as the unit of analysis.

### 3 What Do We Know About Biomedical Innovation?

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This Chapter presents a review of the biomedical innovation literature<sup>46</sup> and, in doing so, facilitates a deconstruction of drug development as a process defined by the actors and resources that surround it. Innovation is, distinct from invention, the commercialisation and exploitation of new ideas (Freeman and Soete, 1997:6). This involves not only the outcome of innovation but also the process leading to the outcome. Accordingly, this thesis is focused on the development of innovative drugs, examining both those that succeed in being commercialised and those that are unsuccessful.

Innovation can be used to describe a product or process, radical or incremental, and technological or organisational (Tidd et al., 1997). This thesis, which investigates biomedical innovation, focuses on technological product innovation that is largely radical and heavily reliant on a strong scientific foundation. In the relationship between science and innovation we observe that theory is a weak guide to practice, whereby R&D is mostly dependent on the 'development' aspect (Pavitt, 1999). This is due to the tacit nature of innovation that accumulates through a process of learning by doing, leading to path dependency at the organisational level.

While broadly speaking innovation is understood as having six common characteristics: uncertain, risky, partly tacit, experimental, distributed, increasingly dependent on a scientific foundation, and regulated (Dosi, 1988), these are amplified in biomedicine. Here innovation is understood to be unique in its highly uncertain, risky and science-intensive nature, as well as the strict regulatory environment it is situated in.

Chapter 2 demonstrated the shifting nature of the system surrounding biomedical innovation over the past 40 years. This has been characterised by an emphasis on the increased specialisation of knowledge, necessitating complex dynamics between

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<sup>46</sup> The search terms used for this literature search were as follows: (biotech\* AND innovation refined for social science, sociology, business economics, social issues, oncology, communication, history, social sciences and other topics, biomedical social sciences, operations research management science, history philosophy of science, science technology other topics); (innovation AND management AND drug AND success); (drug AND success refined for social science, sociology, business economics, social issues, oncology, communication, history, social sciences and other topics, biomedical social sciences, operations research management science); and (pharma\* AND innovation refined for social science, sociology, business economics, social issues, oncology, communication, history, social sciences and other topics, biomedical social sciences, operations research management science, history philosophy of science, science technology other topics). In addition, papers with 20 or more citations were assessed in order to facilitate a focused and systematic literature review while gaining accounting for the articles with the largest impact.

organisations and division of labour. In this Chapter we take this discussion further by investigating the literature that has attempted to explain these dynamics in accessing knowledge and resources, and in directing the progress of innovation. In doing so this Chapter will discuss the key actors influential in defining the success or failure of a drug development project.

The literature review provides an avenue for highlighting the key characteristics and mechanisms influencing innovation direction and outcomes. These are categorised into four conditions and discussed in the final section of this Chapter. These are:

- knowledge base
- market demand
- stakeholder perspectives
- organisational environment.

These conditions comprise the framework that will be implemented to guide data collection and analysis. Furthermore, we introduce the concept of 'project drag' which is used to describe the process by which influential factors act on innovation causing projects to gain, or lose momentum.

The following review highlights two gaps in the existing literature. Firstly, studies tend to be limited to one of two dimensions of analysis, focusing on the innovation impact of organisations, and their networks and/or individuals, and their networks. In an attempt to fill this gap, this thesis implements a multi-dimensional approach, considering a holistic picture of the environment surrounding, and influencing, innovations, including organisation, network and individuals levels. These subsections give structure to the Chapter.

The second gap identified in this literature review is a concentration on organisations and the environmental forces indirectly influencing innovations, through the ability of a firm to innovate. Therefore there is a need to take the innovation as the unit of analysis in order to fully appreciate the environmental dynamics influencing project success and failure.

### **3.1 Organisational Level Dynamics in Biomedical Innovation**

One of the key developments in innovation studies has been in the appreciation of innovation as highly complex and interactive. In this there has been a shift towards a focus on innovations as dynamic, cumulative, path-dependent and the subject of evolution involving selection pressures (Nelson and Winter, 1982). Evolutionary

economics began a tradition of emphasising knowledge and learning in the innovation process, where innovations are reliant, not only on physical resources and tangible assets, but also on intangible capabilities embedded in people, their knowledge, and the integration of this.

Much of the biomedical innovation literature focuses on innovation performance within the firm, organisational performance and competitive advantage. The focus of this thesis is at the project level, however, as most of the literature focuses on the influence of forces on innovations through firm boundaries, it is necessary to consider literature investigating organisational dynamics. Here we focus on the organisation as a mediator, and therefore forces acting on firm performance and competitive advantage, as an avenue to understand project dynamics.

This literature tends to draw on three main approaches. Firstly, the resource-based view, where a key asset of a firm's competitive advantage lies in the resources, both tangible and intangible, they possess (Barney, 1991). Secondly, the dynamic capabilities approach, where there is an emphasis on the firm's ability to develop and use the resources they have, highlighting the importance of internal technological, organisational and managerial processes (Teece et al., 1997). Finally, the knowledge-based view, where organisational performance and competitive advantage are associated with a firm's knowledge base, its ability to create new knowledge and integrate knowledge from outside organisational boundaries (Bierly and Chakrabarti, 1996b, Bierly and Chakrabarti, 1996a, Grant, 1996).

The distributed, tacit and science-based nature of innovation justifies the following discussion which will focus on the sources and integration of knowledge, with an appreciation of the level of specialisation and division of labour acknowledged in Chapter 2. This section is structured in line with discussions of resources enabling innovation, including assets, access to funding, knowledge and the ability to integrate and transfer that knowledge. We are firstly concerned with internal dynamics of these resources, and secondly, the external. This facilitates the identification of particular characteristics and mechanisms that contribute towards innovation outcomes.

### **3.1.1 Internal Dynamics, Knowledge and Knowledge Integration**

The biomedical innovation literature frequently discusses firm level characteristics influencing organisation performance and product development. It is these internal dynamics that are the focus of this section, informing the factors warranting observation in the environment surrounding a drug development project.

Size, experience and product portfolio is found to be significant for firms in discussions of economies of scale and scope and the relationship this has with innovation performance. For instance, Henderson and Cockburn (1996) assessed the discovery phases of drug innovation and conclude that size is related to productivity, whereby larger firms enjoy economies of scale and scope and knowledge spillovers contributing to increased patent outputs. In a follow-on paper, however, the authors find that economies of scale are less relevant to the success of drugs in development phases (Cockburn and Henderson, 2001).

In addition to the relationship between firm size and economies of scale and scope, other studies have emphasised the impact of knowledge spillovers, in terms of experience (Macher and Boerner, 2006), and depth and breadth of product portfolio (Sorescu et al., 2003), on innovation success. Here it is clear that, while size is an important indicator of the extent to which firms can be successful in exploiting economies of scale and scope in innovation, this influence may be mediated by product portfolio and other knowledge dynamics.

Size and economies of scope are also relevant to discussions of asset accumulation from internal and external knowledge sourcing strategies. Here in large pharma the interdependence of technologies influences the accumulation of assets. For instance, the influence of the utility of chemical libraries on the introduction of high throughput screening technologies (Thomke and Kuemmerle, 2002). However, larger firms have difficulties integrating external assets due to the structural inertia that exists (Thomke and Kuemmerle, 2002). This contributes towards stability in the industry whereby, although large firms are reliant on smaller biotech for access to new technological expertise, large firms cannot be displaced due to the complementarity between old and new technologies, and technological approaches.

The impact of size, product portfolio and technological capabilities on organisational innovation potential provides evidence supporting the benefits in capitalising on the characteristics of a firm to facilitate performance. In addition to the critical role of small firms in providing access to new specialist knowledge and technologies (as demonstrated in Chapter 2), there is a critical role of large firms in the drug development process, due to the associated economies of scope and scale, experience, knowledge spillovers and older technologies and capabilities.

However, the reciprocity between large and small firms, and the positive influence this has on innovation relies on the ability of firms to gain access to the resources that facilitate their ability to innovate. Studies show a cyclical relationship between resources,

capabilities and funding in both stock-market offerings and access to venture capital (Deeds et al., 1997, Baum and Silverman, 2004). The factors contributing towards a successful initial public offering (IPO) were shown, by Deeds and colleagues (1997), to be scientific capabilities, such as number of products under development, number of patents, R&D expenditure, location, and quality of R&D staff. In addition, where venture capital funding is assumed to allow firms access to credibility, funding and management capabilities (Niosi, 2003), Baum and Silverman (2004) found that not only did VC contribute towards the performance of firms, but that VC's picked winners, as well as building them up. Small firms are vulnerable to these dynamics particularly due to their tendency to lack profitability, and the resultant reliance on external sources

Due to its dispersed nature innovation is dependent on access to knowledge (explored in the following section) and on the internal capabilities contributing towards the integration and absorption of that knowledge. Here, the concept of 'absorptive capacity' is significant. This refers to the ability of a firm to apply new knowledge from external sources (Cohen and Levinthal, 1990), and is dependent on internal R&D capabilities, whereby a foundation of knowledge is required to facilitate learning from, and develop new knowledge (Cohen and Levinthal, 1990, Gambardella, 1992). In turn, absorptive capacity has been found to improve external knowledge flows and thereby stimulate innovation contributing to the competitive advantage of firms (Escribano et al., 2009).

Several studies have attempted to investigate the factors that contribute to absorptive capacity in life sciences firms. For instance, Fabrizio (2009) associates absorptive capacity with the accumulation of basic research through links with universities contributing to the improved search for new, and good quality, inventions. Another study has shown the importance of size and experience in contributing towards a firm's absorptive capacity (Van Wijk et al., 2008). This evidence implies that larger, more experienced firms would hold a higher absorptive capacity than smaller firms.

This is complicated, however, with Lane and Lubatkin's (1998) conception of 'relative absorptive capacity'. Here, there is an emphasis on the similarities of firms' knowledge bases, organisational structures and research communities, in contributing towards the organisational learning that occurs between firms. This may be explained by the observation that cultural and institutional differences complicate the transferral of knowledge between organisations (Bstieler and Hemmert, 2010). The similarity of firms' stocks of knowledge and knowledge dynamics has also been found to be significant in the selection of partners for collaborative relationships between firms (Baum et al., 2010). This adds a depth of complexity as it implies that despite large firms having the

experience and internal R&D capabilities for building an absorptive capacity, they may still incur difficulties when integrating knowledge from small firms due to cultural and institutional differences.

The degree to which a firm has an absorptive capacity is significant in this thesis as it allows for the development of a proxy to indicate the extent to which a firm would be expected to be able to absorb project related knowledge in the case of collaborative, acquisition and licensing agreements.

Knowledge can be broadly distinguished into two types: tacit and codified knowledge. The transfer of knowledge is dependent on the types of knowledge being transferred and how easily it can be communicated, interpreted and absorbed (Kogut and Zander, 1992). Innovation is largely based on tacit knowledge, particularly if radical. However, the codification of tacit knowledge is not simple, where ambiguity (Van Wijk et al., 2008), problem structure (Macher and Boerner, 2012) and modularity (Pisano, 2006) have been highlighted as central issues. The transfer of tacit knowledge is problematic and involves a high level of interaction, coordination and communication (Pavitt, 1999).

Due to these complexities in the dynamics and characteristics of knowledge, the location of R&D, both within and between firms, is an influential factor in innovation productivity. Here, we observe that in the transferral of knowledge between and within firms, particularly when this knowledge comprises a high level of tacit knowledge, requires extensive communication, coordination and interaction between actors.

Knowledge transfer and innovation within big pharma is also influenced by the location of R&D facilities, where some organisations have shifted towards decentralised models. This shift involves the evolution of smaller autonomous centres involved in R&D activities, aiming to replace bureaucratic control with market control (Jones, 2000). This process of decentralisation of R&D facilities has been observed to be both beneficial and problematic to innovation. Former CEO of GSK observes that decentralisation enables the shift of responsibility for innovation management to scientists who have the passion and creativity necessary for R&D (Garnier, 2008).

However, where centrality in the presence of a broad R&D capability facilitates the development of absorptive capacity (Zhang et al., 2007), decentralisation proves problematic to the transferral of tacit knowledge which requires an understanding of the context of knowledge production and accumulation (Leiponen and Helfat, 2011). While this highlights the need for coordination and communication in decentralised organisations (Leiponen and Helfat, 2011), there are also implications on the type of



innovation that will be produced. Decentralisation may be beneficial to making improvements to existing drugs, or increasing the number of new patents, but it has a negative impact on the production of new drugs (Cardinal and Hatfield, 2000, Leiponen and Helfat, 2011). The level of centralisation of R&D processes influences innovation through a process by which knowledge resources can be transferred.

In this section of the literature review we have discussed the studies undertaken on an organisational level where access to, and dynamics in, internal resources have been the focus. Much of this literature has focused on characteristics of firms that facilitate their ability to innovate. Here, the ability to exploit economies of scale and scope, the production of knowledge efficiently and the extent to which this knowledge spills over were found to be influenced by the size and experience of firms. In addition, the ability for firms to absorb new knowledge was also found to be associated with experience and internal R&D capabilities, however the similarities between firms was also found to be significant. Due to the complex nature of knowledge, it was observed that high levels of communication, coordination and interaction are required to facilitate knowledge transfer processes, which are influenced by the level of decentralisation of R&D in larger firms.

In the context of biomedical innovation, and the establishment of new specialised biotech firms since the 1970s, and the resultant reciprocity in the relationship between organisations in the industry knowledge transfer is an important consideration. Here we observed characteristics of organisations and relationships that tend to facilitate this process. In addition, as we have highlighted in smaller firms, resource vulnerabilities can be detrimental to the innovation process, both in financial and knowledge-based assets. These observations provide guidance to the case histories that follow (Chapters 6 and 7) whereby they have highlighted the types of characteristics that would be expected to facilitate the success of innovative activities.

### **3.1.2 External sources of knowledge**

As highlighted above, access to knowledge is a key determinant of innovative activity in firms. There are two distinct processes that can contribute towards providing external knowledge for firms: collaborations and mergers and acquisitions (M&A). These discussions are particularly significant in this thesis due to the observation that no one firm has all of the capabilities necessary for innovation development. In the biomedical innovation literature there has been a large disparity in the distribution of studies, with a large majority focusing on collaborative strategies and relationships.

This section will divide discussion between these two options of accessing external knowledge (collaborations and M&A). The studies focusing on collaborative relationships

are more extensive, although lessons can be drawn from these to discussions of M&A. The collaboration section covers three areas: 1) the context and roles of collaborations, 2) the specific nuances in different organisations involved in collaborations and 3) the factors contributing towards the performance of collaborations. In doing so this section highlights the characteristics of collaborative and M&A relationships that facilitate, and impede innovation.

As mentioned in Chapter 2, collaborations became a key strategy in biomedical innovation in the wake of the introduction of new technologies and processes in the production of new drugs and the associated rise of a new business model in the form of new biotech firms. The knowledge supporting new product development in biomedicine is, therefore, increasingly complex and multi-disciplinary where innovation tends to begin in smaller firms lacking in commercialisation expertise, requiring larger firms, who struggle to collaborate with universities and thereby miss out on accessing new scientific discoveries (Arora and Gambardella, 1994, Shan et al., 1994). The result of this is the emergence of an open innovation model in the industry (Bianchi et al., 2011). This also allowed for a departure away from the reliance on a vertical integration model for small firms, enabling them to focus on technological and knowledge specialisation (Whittaker and Bower, 1994)

Here, in addition to technological knowledge, small biotech firms require access to complementary assets, (i.e. the necessary capabilities for the global commercialisation, marketing and sales required for successful appropriation of returns from innovations (Teece, 1986)) in order to introduce new products and grow (Nerkar and Roberts, 2004).

In addition to the difficulties associated with small firms having sufficient economies of scale for large scale commercialisation strategies, collaborations for complementary assets are also motivated by the transaction costs associated with environmental barriers such as regulatory pressures (Greis et al., 1995).

As mentioned in Chapter 2 the progression of collaborative relationships between organisations involved in the drug discovery and development process tend to follow a predictable pattern from universities to biotech to pharma firms. One of the reasons behind this is the role of biotech firms as an intermediary, in part due to the institutional and cultural differences between universities and big pharma (Pisano, 2006, Stuart et al., 2007). For instance, where industry are focused on profit generating as a primary motivation for innovation, academic scientists tend to be focused on scientific discoveries, knowledge production and career advancement (Montaner et al., 2001). These cultural

differences can make it difficult for knowledge to be transferred from one actor to another, thereby necessitating the role of a biotech mediator.

This is reminiscent of the arguments put forward by Lane and Lubatkin (1998) who highlight the importance of similarities of firm characteristics in developing absorptive capacity and the difficulties of organisational and institutional differences in knowledge transfer (Bstieler and Hemmert, 2010). Furthermore, collaborative research efforts between scientists at universities and biotech do not often take the form of formal market contracts involving informal networks that facilitate a level of flexibility not always possible in larger firms (Liebeskind et al., 1996). This further supports the idea that biotech-university linkages tend to be more straightforward than those between universities and pharma.

Furthermore, with the frequency of academic entrepreneurs and the increasing pattern of university spin-offs, boundaries between universities and biotech firms are being blurred and broken down (Fontes, 2005, Powers and McDougall, 2005). This highlights the facilitation of collaborations between universities and biotech.

In addition to cultural and institutional differences, information asymmetries, uncertainty and transaction costs have been found to inhibit the collaborative behaviour of smaller firms proving problematic in organisations so reliant on R&D and external knowledge (Audretsch and Feldman, 2003). Asymmetries in information, particularly in terms of experience in undertaking collaborative alliances, also influences the deals biotech companies can access with substantially discounted payments associated with the first initiation of an alliance by a new firm (Nicholson et al., 2005). This further highlights issues that can occur when collaborative relationships are undertaken to progress a drug project.

Additional factors found to influence the performance of collaborations, and therefore the outcome of an innovation include: 1) the timing of the alliance (Danzon et al., 2005), too early and the firm loses the benefits of innovation, too late and a biotech partner may undergo cash flow issues, and 2) the experience of undertaking alliances, and in particular, partner-specific alliances. This final point is, however, contentious with Hoang and Rothaermel (2005) showing no relationship between experience and innovation performance while Wuyts and colleagues (2004) do identify an association.

In addition, in an indirect relationship with innovation performance through the action of the transfer of knowledge, trust is also found to be significant in collaborations (Nielsen and Nielsen, 2009). Furthermore, cooperation between partners also has a role in

knowledge transfer and the effective working of a collaborative relationship. In this, trust and control have been shown to be key to efficient partner cooperation (Das and Teng, 1998).

So far this section has explored the literature describing the dynamics of collaborative relationships and the factors typically observed to be influencing the performance of such a relationship. When putting the dynamics of collaborations together, networks of alliances begin to be appreciated. Here, characteristics of the network have been found to influence its innovation performance.

These characteristics include: the technological distance between the partners, the firm's network centrality and the density of the network (i.e. how closely linked actors in the network are to each other) (Gilsing and Nooteboom, 2006, Hagedoorn et al., 2006). In addition, while direct linkages between firms are important in the innovation network, indirect linkages also play an important role in connecting firms and allowing for greater access to new information and opportunities (Salman and Saives, 2005).

One mechanism in this process is that of the production and fostering of social capital<sup>47</sup>. By representing the resources available in a network, or in specific relationships, social capital has been shown to be a key contributory factor in the development of coordination and creativity (Nahapiet and Ghoshal, 1998), highlighting the distinct and important role it plays in facilitating (particularly tacit) knowledge transfer. Social capital is found to be a significant and important resource for biotech start-ups to build effective cooperative behaviour with partners (Walker et al., 1997).

Social capital is also significant in the relationship between innovation performance and the activities of managers (Moran, 2005). In this argument, both structural (access to people and knowledge, access to opportunities, sales performance and reliance on tangible assets) and relational (closeness, trust, innovation performance and interpersonal relations) embeddedness are found to be important considerations (Moran, 2005).

The cohesiveness of a network can be measured through its density, (Scott, 2000). Density presents the proportion of all possible social ties between individuals that are

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<sup>47</sup> The sum of actual and potential resources embedded within, available through and derived from the network of relationships possessed by an individual or social unit (Nahapiet and Ghoshal, 1998)

observed, and has been found to be related to team performance and commitment of a team to stay together (Balkundi and Harrison, 2006, Reagans and Zuckerman, 2001)

In the alternative form of accessing external knowledge, mergers and acquisitions (M&A) have also been discussed in the biomedical innovation literature. Where M&A are a frequent occurrence in the life cycle of biotech firms, it is necessary, to discuss the impact these events have on drug development.

M&A is often found to be detrimental to innovation, being described as a 'poison pill' (Hitt et al., 1991a), and a distraction for managers of innovation (Ernst and Vitt, 2000, James, 2002). This has also been associated with firm-level path-dependence and organisation-specific routines where the tacit nature and social embeddedness of capabilities means that they are sensitive to change (James, 2002). In addition, firms commonly undertake M&A strategies in times of desperation where they acquire new firms in order to replenish their pipeline (Higgins and Rodriguez, 2006).

However, investigation of M&A events and their influence on biomedical innovation warrants further exploration into mechanisms associated with this negative impact. Firstly, like collaborative relationships and the integration of external knowledge into firms, the performance of M&A depends on the internal knowledge capacity of the acquiring firm (Ahuja and Katila, 2001).

In addition, the similarity of the knowledge bases of the target and acquiring firm has also been found to be important to M&A success (Mowery et al., 1996, Prabhu et al., 2005), as has the knowledge an acquiring firm has about the target firm, prior to acquisition (Higgins and Rodriguez, 2006). Larger firms with more diverse capabilities in product development and downstream commercialisation assets have been found to be better at M&A, whereby product capital (product development and support assets) is a significant factor in acquisition performance.

In acquisitions, post-event knowledge transfer has been shown to be enhanced by communication, visits, meetings and the time since the acquisition took place (Bresman et al., 1999). In addition, knowledge transfer has also been shown to be reliant on trust, strong relationships and shared visions to overcome common issues associated with tacit knowledge and cultural differences (Van Wijk et al., 2008).

The level of integration involved in an acquisition, whereby on the one hand a firm may acquire another but not integrate it into the organisation, and on the other, the target firm may be fully integrated, is also found to influence the level of performance of the acquisition (Paruchuri et al., 2006). Here, one study found differences in research

expertise of the two firms impacted integration to cause the greatest disruption to innovation (Paruchuri et al., 2006). Another emphasizes the importance having different integration approaches dependent on the position of the acquired business in the value chain, with R&D entities maintaining a degree of autonomy post-acquisition (Schweizer, 2005).

### **3.1.3 Organisational Level Summary**

In summary, this section has provided an overview of the literature concerning the dynamics of external sources of knowledge in the form of collaborations and M&A, taking into consideration the distributed, science-based and tacit nature of innovation. In doing so we can begin to highlight mechanisms by which collaborative relationships and M&A events impact innovation.

Firstly we built on discussions from Chapter 2 in demonstrating the reciprocal relationship that has been built between the main actors in drug discovery and development, pharma, universities and biotech. Here, we discussed the difficulties in collaborations between organisations that show particular cultural and institutional differences, for instance, pharma and universities. Here one mechanism for mediating this effect is in the use of biotech firms as an intermediary. We discussed the performance factors associated with collaborative relationships and the role of the network location and relationships of an organisation, for instance, in the facilitation of the formation of social capital between actors.

The literature on M&A in part replicates the concepts from the previous sections in terms of emphasising the difficulties in knowledge transfer. In addition, the integration of the acquired firm into the enlarged organisation was also found to be a significant factor in determining the success of the acquisition. This literature is of particular significance as M&A events can be interpreted to be problematic for innovation, and drug projects, due to the organisational environment they create.

## **3.2 Individual Level Influences on Innovation**

So far in this Chapter we have recognised the importance of resource support for innovations, on an organisational and inter-organisational level. This access to resources, including knowledge is particularly salient when we reconsider the distributed, science-based, uncertain and tacit nature of innovation. As this section demonstrates is also necessary to consider this, and the support innovations get, on an individual level. This is particularly important due to the key role played by individuals, in shaping the direction of innovation within organisations.

This discussion will focus on individuals both within and outside the project team, where innovations can be influenced in a number of directions by the stakeholders that surround it. This section will focus on the mechanisms by which individuals can shape technologies, thereby impacting their success, or failure, and the nature and characteristics of these individuals, and networks, or groups of individuals.

Individual level influences on innovation can be split into three areas: 1) the action of key individuals, 2) the interaction between academic scientists and industry, and 3) network positions of individuals and the influence this has on the ability to create and absorb the knowledge necessary for innovative activities.

### **3.2.1 Key Individuals – Characteristics and Impact on Innovation**

The literature around the idea that key individuals may impact the progression of innovations began with the idea of ‘champions’<sup>48</sup>, highlighting the role of individuals reducing resistance to radical innovations allowing for adoption (Schon, 1963). While it is intuitive that most innovative projects will involve of key individuals, it is the action and characteristics of these people that define the nature of their influence on innovation.

Early definitions of champions highlighted a direct link to innovation success. Here they were described as individuals that ‘make a decisive contribution to the innovation actively and enthusiastically, promoting its progress through critical stages’ (Rothwell et al., 1974, Rothwell, 1992). Champions influence innovation by expressing enthusiasm and confidence for a project, getting people involved and persisting under adversity (Howell et al., 2005, Rothwell, 1992).

Additional characteristics associated with successful champions include: 1) pursuing innovative ideas, 2) network building, 3) persisting under adversity and 4) taking responsibility for the idea (Walter et al., 2011). In addition, in leadership skills, key individuals responsible for managing creative individuals are found to have technical prowess and an ability to get people to work together (Mumford et al., 2002). Common personality traits found to be associated with champions, include leadership qualities, charisma, confidence and inspiration (Howell and Higgins, 1990).

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<sup>48</sup> The term ‘champions’ fell out of favour in innovation studies, due to the difficulty in defining the concept and the variety in the actions and characteristics of different individuals, and their influence on innovation. Despite this section reviewing the literature on champions and thereby using this terminology, in general in this thesis we will refer to ‘key individuals’.

The diversity of skills necessary for key individuals to be influential is akin to the term 'heterogeneous engineers', whereby in order to be successful innovators must act as 'system builders' reshaping the social world that surrounds the innovation (Law, 1987).

Champions have a direct impact on innovation projects and programmes, while indirectly impacting firm performance (Markham and Griffin, 1998). It has also been observed that champions can have a negative influence by backing failures (Markham et al., 1991). In particular, the impact champions have can begin to become dysfunctional producing an inverted U-shape in the relationship between both 'persisting under adversity' and 'taking responsibility, and innovation sales growth' (Walter et al., 2011). This can be explained by the fact that champions will continue to support a project despite potential low performance (Markham, 2000).

Much of the literature has focused on the different types of champions and the skills they need to influence innovation. Firstly, Burgelman (1983) identified the group leader, or venture manager, as requiring knowledge skills (i.e. technical and need linking); a new venture development manager, having persuasion and political skills in strategic building; and a corporate manager, with commercial skills in rationalisation.

In addition categorisations of key individuals include: technical innovators/inventors, business innovators, and chief executives, with the varying levels of influence in promoting innovation, relating to seniority, age, power, and experience (Rothwell et al., 1974, Rothwell, 1992, Freeman, 1997).

The different skills required for roles in innovation are: the inventor, requiring knowledge, a breadth of understanding, ability to problem solve and provide inspiration, motivation and commitment; the organisational sponsor, with power, influence and an ability to pull strings based on belief in the potential of a project, not dependent on in-depth knowledge; the business innovator, providing a user perspective and market implications; and the technological gatekeeper, responsible for collecting information from the network and distributing it within the project group (Tidd and Bessant, 2013:120-122).

In addition, receptiveness is also key to the extent to which a key individual can influence the direction of an innovation. This has been found to be both sector, and organisation specific, whereby larger organisations with hierarchical and bureaucratic structures will be less easily influenced by a champion than smaller organisations with flatter and more flexible structures (Rothwell, 1992, Rothwell et al., 1974). This may be associated with formalisation of processes, i.e. the more formal the structure and processes of an organisation, the smaller the influence by individuals (Markham and Griffin, 1998). In this,



there is a key role of the individual to influence others' values and visions around a project (Van De Ven, 1986).

In this thesis we are interested in noting the characteristics which lend themselves to an individual becoming an advocate for the innovation being developed. For instance, we may observe an inventor who has the technical knowledge, breadth of understanding, motivation and commitment to see a project through from early stages, contributing to overcoming potential issues in development that might arise. In addition, the ability to mobilise resources, both in the organisation, and from networks, is also considered a critical skill of an individual in this context. We apply the term 'project advocate' to encompass these expertise, skills and characteristics of an individual which are critical to differentiating success from failure of the development of drug projects.

Data charting the action of key individuals is largely observed to be anecdotal in nature and therefore generally reliant on post-hoc observations and selection biases towards successful projects (Markham and Griffin, 1998, Howell and Shea, 2006). In a statistical study of the influence of champions, Markham and Griffin (1998) observe a relationship between project and programme performance and the presence of a champion while also supporting an observation by Rothwell (1992), that champions play a role in innovation, but are not sufficient for success. Methodologically the presence of a positive influence of a key individual is perhaps more apparent in empirical data than the absence of influence. Furthermore, key individuals are generally recognised retrospectively, implying the potential for survival bias whereby a range of individuals may have been significant in influencing an innovation, but only one is remembered.

In clinical investigations key individuals (clinical investigators) have been shown to promote the development of purine analogues by diversifying the range of indications the drugs were trialled in: 'clinicians treating a particular disease and not the company producing the chemical entity may be the primary drivers of drug development' (Flowers and Melmon, 1997:138). Furthermore, the action of clinical champions is directly linked with overcoming issues associated with lack of resources and limitations in relevant disease understanding (*ibid*).

Flowers and Melmon (1999) ascribe the success of champions to their roles in pushing the projects through development, rather than projects being pulled from clinical need. Despite this study lacking an explanatory link between success and the role of the champion, as exemplified in project SAPPHO (Rothwell et al., 1974), it is clear from this that champions do have a role to play in the development of biomedical innovations.

In this section the characteristics and nature of the influence key individuals have on innovation have been demonstrated. In particular, we observe the ability for an individual to promote a project throughout development utilising particular skills, resources and characteristics. However, we have also discussed the limitation of the concept and suggested some ways in which different typologies can be used to improve the utility of it. Furthermore, we have highlighted the importance of identifying common characteristics, personality traits and activities, due to the methodological difficulties in observing the phenomenon.

### **3.2.2 Key individuals and Networks**

This section will explore the influence of individuals' networks interactions on innovation success. This discussion further appreciates the distributed nature of innovation, in individuals, where previous discussion has centred on distribution among organisations. The previous section highlighted the importance of structural characteristics that enable individuals to become key to the innovation process. One of these was the relationships between an individual and his or her network. Here motivations to collaborate, the nature of relationships, and how these relationships are formed, are found to be noteworthy.

The motivation of academic scientists influences innovation due to their willingness to work with others outside academia. Furthermore, it is important to consider the output objectives held by individuals as alignment between these and those of industrial partners can be key in influencing success. University scientists have been found to be motivated to partake in joint research, contract research and consulting, by research-related motives, however, somewhat predictably, the formation of patents and spin-outs are associated with commercialisation motivations (D'Este and Perkmann, 2011). Furthermore, interactions with commercial scientists have an impact on the desire of university scientists to become entrepreneurs (i.e. start a spin-out company) (Stuart and Ding, 2006).

The motivations for industry to interact with academic labs is associated with the presence of 'scientific capital' (i.e. the intellectual capital, academic tenure, research settings and human capital contributing towards the accumulation of learning processes in collaborative relationships) and the presence of post-docs in research labs, providing an indicator of credibility, quality and the potential for future collaborations (Oliver, 2004).

In defining and developing relationships, there is a role of key individuals in building trust and governing collaborative relationships in university-industry collaborations (Bstieler et al., 2015). Here relationships are encouraged by key individuals, in particular, in

supporting discussions around intellectual property and governance issues (Bstieler et al., 2015).

Another example of the way in which key individuals act to facilitate relationships, demonstrated in discussions of interferon- $\alpha$  (Gutterman, 1997), highlights the critical role of key individuals (in this case the clinical discoverers) in promoting a research agenda to bring together and facilitate cooperation between the public sector, private sector and academia. This idea relates to that discussed above, wherein an individual's network prove to be key in enabling innovation.

Structurally the location of key individuals in the network impacts the relationships between organisations, the information flows facilitated and the impact on innovation performance. Firstly the centrality of inventors within the firm network has a mediating effect on information flows, resulting in an inverted U-shape relationship between centrality and innovation activities (Paruchuri, 2010). Key individuals also act as gatekeepers and boundary spanners between university and industry, facilitating interactions between these two institutional cultures (Breschi and Catalini, 2010, Hess and Rothaermel, 2011).

The nature of the interactions between scientists is also important in networks of individuals and their impact on innovation. In this, the role of a corporate core scientist (defined by having high numbers of publications and citations) is key to absorptive capacity, due to their position in occupying channels through which knowledge flows to researchers (Furukawa and Goto, 2006). Furthermore, interestingly these scientists are not themselves integral to the patenting behaviour of firms but act to promote patent applications of co-authors (Furukawa and Goto, 2006).

This section has taken the discussion of the impact individuals have on innovation further, by reviewing the literature exploring the nature of the networks of individuals and the action these networks have. Here we have shown that motivations for collaboration depend on the output of the relationship from the academic perspective, and on the credibility of the research group, from the industrial partner perspective. Aligning these objectives would be expected to contribute towards a smooth working relationship. We find evidence supporting the previous observation that, position in, and nature of, a researcher's network enables the action of individuals in positively contributing towards innovation success. The review of this literature has highlighted some key characteristics of individuals and networks and mechanisms by which innovation is influenced.

### 3.2.3 Expectations – Who Constructs Innovation and How?

Expectations are diverse and take the form of ‘visions’ or ‘promises’, composed of ‘hopes and fears’, ‘wishes and desires’ (Koch, 2006). They can be individual or collective (Borup et al., 2006, Berkhout, 2006, Konrad, 2006), change over time (Brown and Michael, 2003, Borup et al., 2006, Berkhout, 2006), and depend on the situation of the actor (or stakeholder) in relation to the technology in question (Brown and Michael, 2003, Konrad, 2006).

Promises, visions and expectations are key to innovation due to its future-oriented nature (Borup et al., 2006). In particular, in radical innovation where there is a lack of previously evidenced utility, expectations are important in overcoming the inherent high uncertainty (Brown and Michael, 2003, van Lente and Rip, 1998). In our discussion of individuals and their influence on the progression and direction of innovation it is necessary to discuss expectations as a mechanism by which this influence occurs.

Several of the main functions of expectations, in the influence they have on innovative activities, are reliant on shared visions. These are: 1) the ability for expectations to coordinate research efforts, 2) the mobilisation of resources, 3) the maintenance of networks by brokering relationships and 4) promotion of research directions (Brown and Michael, 2003, Borup et al., 2006, Konrad, 2006). These processes have a direct influence on innovation, through both individual and collective expectations within firms, and visions to motivate and set the pace of innovative activity (Borup et al., 2006, Konrad, 2006).

Expectations are also key in leadership, as observed in Paul Janssen manager of Janssen Pharmaceutica. Here, a successful management style is characterised as giving scientists freedom, encouraging probing activities while focusing efforts on achievable goals (Lewi and Smith, 2007). Another leadership behaviour, termed ‘transformational leadership’, is described as promoting individual interests of leaders and followers, motivating the action of emotions, emotional links and values, encouraging creativity, visions of a shared mission, direction and innovation culture (García - Morales et al., 2008)

On an individual level, expectations, due to the direct link with uncertainty, may vary in accordance with the proximity of the individual to the production of knowledge surrounding an innovation (Brown and Michael, 2003, Sung and Hopkins, 2006, Konrad, 2006). This is perceived not only because the actor closer to the innovation will have more knowledge about the potential for failure (information asymmetries), but also it is

likely that they will also have experience of past failures which may influence their expectations (Brown and Michael, 2003, Koch, 2006). Furthermore, in the case where the actor has vested interest in an innovation, i.e. they may benefit from its success, the expectation produced is likely to be heightened more than where the actor is not set to gain (Konrad, 2006).

Martin et al. (2008) suggest the existence of 'communities of promise' which establish around a technology, in which a shared sense of community, encouraged by the imagination of the research contributing toward the innovation, informs the creation of knowledge and networks. In their work, Martin et al. (2008) describe three epistemic communities surrounding the development of haematopoietic stem cells which each play a role in influencing the development (both in basic science and clinical practice) of the technology.

While expectations are usually associated with positive influences on innovation, uncertainty can lead to issues that cause actors to become disappointed (Borup et al., 2006, Sung and Hopkins, 2006, Konrad, 2006). Here, expectations influence innovation through the creation of protected spaces arising from the embedding of shared expectations amongst actors, or communities of promise (Martin et al. 2008). This, and a process of lock-in, leads to the suspension of evaluation criteria, contributing towards results being interpreted subjectively (Konrad, 2006). When disappointment occurs, the protected space collapses, and the evaluation criteria are re-activated (Konrad, 2006).

The concept of protected spaces has also been used in the strategic management literature applied to sustainability transitions (Schot and Geels, 2008, Smith and Raven, 2012). Here, technological niches produce protective spaces for path breaking innovation which facilitate the shielding, nurturing and empowerment, thereby limiting the effect of selection pressures on the development and adoption of the technology (Schot and Geels, 2008).

In this thesis we draw on Konrad's (2006) conception of protected spaces, whereby it is applied not to the societal level but to the formation of collective expectations shared amongst actors within an organisational boundary. We expect small groups/firms to be more affected by the action of protected spaces due to the ease of sharing, embedding and reinforcing shared expectations.

The shift of expectations from the individual to the collective is contributed towards by concept formation, i.e. the sharing of visions required for the dissemination of expectations (Brown and Michael, 2003), and the translation of expectations into a

codified format (Konrad, 2006). The sharing of expectations within a group facilitates mobilisation of more actors producing large cohorts of collective expectation that may eventually become assumptions in society (or in a particular group), thereby feeding back into individual expectations (Konrad, 2006). Here Martin et al. (2008) describe the stabilisation of the 'socio-technical identity' of networks through the sharing of imagined understandings between actors and within communities.

Collective expectations are used by patients and patient groups to influence innovation through raising funds, decision making, trial design and implementation, development of disease registries, conferences, publishing and participatory research, as well as influencing technological trajectories, state politics and organisations and markets (Epstein, 2008). Epstein's (1995) case study of AIDS activists in the 1980s demonstrates how trials for new HIV drugs were reconceptualised to have a dual purpose, both as a scientific experiment but also in healthcare provision. The mechanisms employed to achieve this included: obtaining credibility by learning the relevant terminology, attending conferences, reading and researching and building a basic scientific knowledge base, and taking sides on pre-existing debates (Epstein, 1995). Epstein (1995) also highlights the importance of the established networks and experience spilling over from the gay movement in the preceding decades. It is likely that this involved the development of shared visions and protected spaces, whereby groups of people could mobilise and come together for a collective cause.

Patient groups have also been shown to have had an influence in the development, and post-marketing strategies, of the breast cancer drug, Herceptin<sup>49</sup>. Bazell (1998) describes patient groups putting pressure on Genentech to provide continued access to the drug for patients who had previously been enrolled in phase II trials. This activism was successful and Genentech did make the drug available on a compassionate use basis (Bazell, 1998).

This consideration, of the action of patient advocacy groups is also highlighted in studies by Boon and colleagues (Boon and Moors, 2008, Boon et al., 2010, Boon et al., 2008, Boon et al., 2011). Specifically, the key role played by patient advocacy groups (or intermediary organisations) is stated to be in the articulation of demands by users, both patients and clinicians, to policy makers and producers (Boon et al., 2008, Boon et al., 2011). This is of particular importance when managing expectations and shared visions

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<sup>49</sup> Further discussion of the development of Herceptin is presented in Chapter 5.

of a technology, or in a disease area (Boon and Moors, 2008, Boon et al., 2010). Similarly, Rabeharisoa (2003) adds that the action of patients groups is mediated by their national setting, and the nature of the relationships developed with stakeholders involved in the innovation process.

The relationships between pharma and patients are, however, not uni-directional. As well as patients influencing firms, firms also impact patients' perspectives and policy (Abraham, 2010). Furthermore, pharma have also been found to work with, and provide funding for, patient groups, thereby implying a danger of conflict of interest in the actions of such groups (ibid).

The action of expectations in rallying collective action and in the development of technologies have been demonstrated in membrane technology. Here, development was influenced by the perceptions of it by stakeholders (van Lente and Rip, 1998). Hedgecoe and Martin (2003) also use the role, and characteristics, of expectations and visions, and the stakeholders that possess them, to explain how pharmacogenetics has been over-hyped, despite unsubstantiated claims. The idea that social factors influence individuals' perception was also found to be significant in gene therapy, where a new industry formed around a technology (Martin, 1999), and in pharmacogenomics (Hedgecoe, 2003), where commercial interests and competition acted to shape the construction of the term.

Proxies for the influence expectations have on innovation have been shown to include concept formation and the media. Concept formation has been operationalised by measuring the dynamics found in the mentions of particular technologies in encyclopaedias (Koch, 2006), allowing perceptions to be recorded over an extended period of time. The media is taken as a representation of the collective expectations surrounding a technology (Konrad, 2006). Furthermore, the media is seen to be the traditional mode of scientific communication, facilitating the diffusion and dissemination of information and discoveries to the public (Lewenstein, 1995).

### **3.2.4 Individual Level Summary**

This section has highlighted mechanisms by which stakeholders' individual and collective expectations can formulate to influence the outcome of innovation concluding the discussion of the role of project advocates in the innovation process. This section has focused on drawing out characteristics and mechanisms by which individuals, their networks, relationships and expectations influence innovation success. We use these observations to guide and interpret the data collected in the empirical analysis of this thesis, in the discussion of drug project case histories. In particular, we would expect that

individuals who are invested in the development of a drug project, for instance, by inventing it or being involved from very early stages, or for a long period, would have the knowledge, motivation and necessary access to resources to contribute towards overcoming potential issues that arise during development.

### **3.3 Multi-dimensional assessment**

This literature review has so far examined the literature focusing on each of the dimensions of innovation: organisation/network level and individual level. In this thesis we will implement a strategy that takes into account a multi-dimensional assessment of the environment surrounding an innovation. While taking the drug project as the unit of analysis, this thesis draws on Rothaermel and Hess (2007) who investigate innovation antecedents on individual (intellectual human capital, star scientists), firm (R&D capability), and network (strategic alliances and acquisitions) levels.

In addition, we observe a similar strategy to that taken by Blume (1992) who uses three case studies and undertakes a holistic (i.e. multi-dimensional) perspective on the influential factors surrounding the development (and adoption) of new technologies.

For the purposes of this thesis we can rationalise that ultimately projects are located within organisational environments; organisations are motivated by returns on investment, strategy, environment (internally and externally) and knowledge accumulation. Individuals make up organisations. Therefore, organisations are also motivated by conditions other than return on investment, such as interpersonal relationships, and organisational dynamics, but also on self-promotion, knowledge and networks. Organisations and individuals are part of networks. Networks are the loci of resource exchange and transfer (resources include intangible assets, such as knowledge, and tangible assets, such as finance and equipment). Users and other individual stakeholders are also involved in the networks surrounding projects. These include public opinion which can influence organisation decisions but also may influence individual perspectives within the organisation or more widely in the network. This provides the foundation on how the different elements of the multi-dimensional approach might fit together.

In this thesis we take on a matrix approach whereby we integrate a multi-dimensional approach with a framework that will guide the investigation into project development by identifying the conditions contributing towards the progression (trajectory) of a drug project. The construction of this framework is the main aim of the following sections of this Chapter.



### **3.4 Success Factors – Developing a Framework**

This section highlights the environmental conditions created by innovation actors that exist to surround and influence the project, either through a process of project drag, where issues accumulate to contribute towards momentum or, in defining definitive go/no-go decisions.

Project SAPPHO (1970s) was one of the first studies to appreciate a multi-faceted approach to innovation outcomes by focusing on the factors influencing successful, and unsuccessful, innovations (Rothwell et al., 1974). The main internal and external influencing factors highlighted were: user needs, efficiency of development, characteristics of managers, efficiency of communications, marketing and sales, and industry-context (ibid). However, some of these have clear relation to the adoption and dissemination of technologies, as opposed to the development phases, as is the concern of this thesis.

In biomedical innovation Blume (1992) draws on a range of disciplines to explain the development (and adoption) of imaging technologies. In order to do this Blume (1992) suggests a framework allowing a researcher to investigate a technology, by consideration of a) the interorganisational structure, namely, the relationships between the producers and users of a product, b) the career of an innovation, breaking development and adoption of the product into phases to allow for cross case comparison, and c) problematisation, or the extent to which issues in the development and adoption of a technology are resolved and how this effects the progression of the technology.

Blume's (1992) framework is drawn on in this thesis, whereby the interorganisational structure (as per Blume) is represented in the multidimensional perspective accounting for the multitude of actors involved in innovation, as per the preceding sections. The career is accounted for where the empirical evidence of this thesis is provided as a chronological narrative encapsulating the development of the drug project. Furthermore, and the problematisation is represented in the suggestion of certain issues ('downers') that cause delays and influence the decision of whether to discontinue a project or not (as discussed in the following paragraphs). In this Blume (1992) suggests looking at the questions posed in the development of technologies and the resources (or capabilities) used to deal with them.

This thesis introduces a key concept, that of 'project drag'. This construct is associated with the perception of 'projects' as future oriented endeavours with their own momentum (Nightingale et al., 2011). This creates a perception that conditions contribute towards

the 'drag' of a project throughout the life-cycle gradually contributing towards the project stalling, and thereby being terminated.

Project drag describes the process by which issues that detract from the business case for developing a project accumulate, moving towards and in some cases culminating in a decision to discontinue. As opposed to distinct go/no-go decision making, project drag identifies a series of perhaps individually small issues, that independently would not cause termination, which are amplified when found in the presence of other negative occurrences. For example, they may be contextual and unrelated to the drug itself.

Drawing on the aforementioned organisational dynamics and knowledge transfer literature, project drag conceptualises the issues accumulated during the movement of drug projects from organisation to organisation during licensing agreements and M&A, for instance. In addition, re-evaluation of drug projects in a new acquiring or licensing company, may contribute to increasing project drag.

Furthermore, as we will see, conditions associated with the success or failure of a drug project may contribute towards differing levels of project drag in the various teams involved in drug development. Whereas market demand and any potential associated issues may contribute towards project drag for the marketing and sales team, the extent to which drug development has a strong knowledge base may be of more concern to the scientific project team.

We can also consider the influence of the aforementioned concept of protected spaces balancing with project drag, whereby the perception of the issues contributing towards project drag may vary in different project teams. For instance, where one project team, or epistemic community, which may be small, are working closely together towards a common goal, a protected space may develop which influences the accumulation of project drag. If we assume that knowledge is heterogeneous and assembled around a project we can conclude that the knowledge, which can contribute to success, protected spaces and avoiding project drag, breaks down if the community breaks down, for instance, in response to M&A or other movement between organisations.

Project drag shows some similarities to the concept of 'critical path drag', attributed to Devaux, and used to represent the extent to which something (the critical path item) is delaying the completion of the project (Devaux, 2012). In addition to this time dimension of the progression of a project, 'drag cost' is also used to define the value lost due to the delayed delivery from the critical path drag (ibid). While project drag shows some overlap with the notion of drag costs, i.e. that mounting costs contribute towards decision making,

the concept of project drag emphasises the extent to which external events accumulate allowing an innovation to gain, or lose momentum.

Furthermore, project drag is linked to the idea, from evolutionary economics of path dependency, whereby the outcome of a project, and the pathway it takes, is dependent on the accumulation of historical contexts and past decisions that have influenced it. These ideas will become salient in section 3.3 when we discuss the implications of the framework in terms of the specific issues that may arise and contribute towards decisions.

This thesis adds to Blume's framework by suggesting conditions which should be considered when accounting for the successful (and failed) development of technologies in biomedicine. These relate to the selection environment suggested by the evolutionary economics approach. The selection environment described by Nelson and Winter (1982) provides direct justification for three of the four conditions highlighted from the framework in this thesis: the influence of markets, relating to profits; non-markets, relating to social forces, and the organisational environment within and around firms. Dosi's (1982) contribution focused on the innovation as the unit of analysis where he highlights the influence of the following environmental selection pressures: non-economic, technology, social, institutional, economic and science.

**Table 3 Summary of literature review of studies identifying factors associated with success of innovation in biomedicine**

<b>Authors</b>	<b>Success Factors</b>	<b>Output</b>	<b>Indicator</b>
<b>Siegel and Renko 2012</b>	Market knowledge; technology knowledge	Opportunity selection by entrepreneurs in small firms	New inventions; patent applications
<b>Ahuja et al. 2008</b>	Industry structure; firm characteristics; intra-organisational attributes; institutional influences	Innovation production by firm	Innovation effort and Innovation output
<b>Deeds et al. 1999</b>	Scientific; technological; managerial skills	Innovation production by firm	Products in trials and marketed
<b>Chandy et al. 2006</b>	Speed of idea production; number of ideas; expertise	Conversion of ideas to product	Patents to launched drug products
<b>Blau et al. 2004</b>	Technical success; high development costs; uncertain market impact; scarcity of good new product ideas; human and capital resources	Evaluation and selection of new drugs by firm	New drugs

<b>De Luca et al. 2010</b>	Market orientation; knowledge integration	Innovation production by firm	New products; patents; acquisition of relevant knowledge; good reputation for results; ability to attract outstanding human capital
<b>Khilji et al. 2006</b>	Technology push; market pull; organisational approaches	Biotech manager perspectives	
<b>Nerkar and Shane 2007</b>	Scope; pioneering nature	Innovation production by firm	Patents commercialised
<b>Fetterhoff and Voelkel 2006</b>	Customer insight ; technology awareness	Innovation production by firm	Commercialisation of inventions
<b>Bernstein and Singh 2006</b>	Market pull; technology push; organisational constructs (management, communication, structure, control)	Innovation production by firm	Stage success (idea generation, support, development, implementation)
<b>Moors 2002; Moors 2007</b>	Financial risk, non-financial benefits; image; complexity; trialability	Rare cancer innovation	Drug projects

In addition, this literature review has identified biomedical studies that discuss success factors in innovation (Table 3).

By incorporating the findings from the literature review so far, the following section will discuss the four conditions identified to be significant in influencing the progression of innovation through the drug development process. These factors are considered to influence the selection of a project and the decision as to whether to continue to invest in its progression through to approval phases.

#### 3.4.1 Knowledge Base and Accumulation

The first condition concluded to contribute towards innovation is the extent to which there is foundational and accumulated knowledge surrounding it (project, target and disease).

This is, in part, intuitive, where clearly without some level of technical understanding of a project it would be difficult for it to be fully developed. Studies of biomedical innovation have highlighted this. For instance, Agrawal and Searls (2009) emphasise the importance of scientific inputs by claiming that decisions should align outputs with new therapeutic opportunities. This relates to the knowledge base focused on the disease pathology, disease-target and drug-target interactions.

In knowledge accumulation there is an importance of practice, learning and experience in the development of knowledge bases to support innovation (Nelson and Winter, 1982).

A reliance on knowledge is observed in innovation projects whereby the experimental learning critical to innovation is inhibited by the inability to break problem solving down into incremental steps (Yaqub and Nightingale, 2012).

Knowledge is constructed in the people that produce it and is therefore dependent on the producers and users of knowledge and the expectations they hold. This is dependent on the experience and understanding of a particular drug and therefore relates to the duration over which research has been carried out. Here, uncertainty in new technological areas may be problematic for projects (Nuffield Council on Bioethics, 2012). Issues can occur whereby information asymmetries, common to new areas with small numbers of specialists, can inhibit knowledge sharing and accumulation.

It follows that issues surrounding knowledge transfer and accumulation would be problematic for innovations. This concerns the ability for researchers to come together, interact and develop social capital, which can facilitate the transferral of tacit knowledge (Nahapiet and Ghoshal, 1998, Moran, 2005). Furthermore, the integration of knowledge by a firm, or research team, is reliant on their R&D experience, and understanding of the project and/or target (Cohen and Levinthal, 1990). Within organisation relationships innovation and knowledge accumulation is facilitated by the development of routines (Nelson and Winter, 1982). However, there is also a risk associated with routines that firms can become subject to lock-in and path dependency that may inhibit learning in new technological areas.

In this section we have highlighted the need to consider both the knowledge base, providing the foundation for a drug development project, and the processes by which knowledge can accumulate. This condition influencing drug development is situated in the scientific research teams involved in drug development. It is these issues that are of concern when considering how this condition influences drug development outcomes. Where we observe that the knowledge surrounding the development of a drug is not fully developed or understood, we anticipate this contributing towards project drag, whereby initially this lack of knowledge may not immediately contribute towards the discontinuation of drug development but over time uncertainties may culminate in confidence around the project being lost.

### **3.4.2 Market Demand**

The second condition is the perceived potential market associated with an innovation. The thesis that market demand was the key driver of innovation was first suggested by Schmookler in the 1960s, who followed longitudinal patterns in patent statistics,

investment and outputs (Schmookler, 1966). Despite heavy criticisms of the 'market pull' linear model (Mowery and Rosenberg, 1979), it is not rejected that market forces do contribute towards defining the direction of innovation. This has been demonstrated in an analysis of trends in R&D expenditure and entry of innovative drugs demonstrating an association with increasing market size (from population growth) (Acemoglu and Linn, 2004, Cerda, 2007, Magazzini et al., 2010).

Market demand can be understood in two ways: 1) in the differing visions of the various stakeholders involved, and 2) by a producer. However, this process is rarely perfect and involves a level of uncertainty particularly in the case of radical innovations.

Conceptualising market demand involves a balance between risks and (potential immediate or future) returns, and the decisions made by firms regarding innovation progression. If there is a larger uncertainty over the commercial potential of a product, i.e. higher financial risk, then the innovating firm might have less inclination to continue development. The uncertainty over project commercial viability is also relevant when considering the difficulty in predicting market demand levels, particularly considering the long development times of drugs, as is seen in oncology.

There are three main issues associated with market demand that can be predicted. The first is low potential market, further complicated by the context of uncertainty and questions of return on investment. Smaller firms may be more accepting of smaller markets because, on the one hand they have less requirement for large profits; on the other, due to the lack of options available to small firms, they tend to be more risk averse. Despite the reliance, of small firms, on VC, who expect high returns, this is not necessarily linked to profits. In contrast, large firms have high fixed costs and are required to make expensive investments into R&D in a diverse range of areas (Nightingale, 2000). Furthermore, smaller firms tend to have fewer resources and therefore benefit from the cost reductions arising from schemes such as fast track and accelerated approval.

Small firms do have a requirement to satisfying their shareholders who may have high expectations of return on investment. However, this should be considered, given that shareholder return comes on exit, which may be on floatation on the stock-market, or on acquisition by pharma. Therefore, the emphasis lies on the perception of market potential by other firms and analysts, which could relate to additional valuation criteria, other than markets.

In addition, proof of concept considerations may also play a role in driving innovation in areas that have a lower market potential. Here, a new technological approach may be explored in a smaller patient population initially with the expectation of a future broader application in larger markets. Indeed this was illustrated in a recent article highlighting that one of the motivations to develop an antisense therapy for the rare disease homozygous familial hypercholesterolemia was a desire for proof of concept (Sinha, 2013).

Another market-related issue is in the potential for patents to expire in the context of projects that are progressing slower than anticipated leading to issues with appropriating returns from investment. This can be partially counteracted by the application for orphan drug status, acting in the same way as patent protection by providing market exclusivity.

Additional considerations highlighted by Tidd and Bessant (2013) and Ahn et al. (2010) are market trend and growth, market share, market risk, pricing trend, expected product sales life, cost savings, and marketing and distribution, as factors that should be considered in product development.

In conclusion, smaller firms may be less constrained by market-related issues while larger firms may consider limitations in expected market demand, as an influential factor implying a risk of termination for the project, leading to a no-go decision. In smaller firms, that may not have vast resource for marketing and sales, market-related decision-makers would be expected to be in close proximity to the scientific research, but have the added complication of shareholder influence on the executive board. In contrast larger firms with established marketing and sales teams show more distance between the scientific endeavour and market-related decision making.

In general, we predict the expiry of patents to be important, as well as competition for the drug and the range of indications it can be applied to. Project drag may occur where competitor drug projects are in development but not yet approved, i.e. as profit margins are increasingly threatened, or as time goes on and patent expiry nears.

### **3.4.3 Stakeholder Perspectives and Expectations**

The third condition concerns how much potential relevant stakeholders, or actors, who surround the drug perceive the innovation to have. This includes the construction of visions that would be expected to influence the perception of an innovation by other stakeholders and firms.

Stakeholder perceptions in the sense described here, may be related to the importance of a strong public image and customer acceptance to firms (Moors et al., 2002, Tidd and Bessant, 2013). This is likely to be more important in larger firms than smaller firms, due to the reliance on public image for the sales and marketing. If particularly negative, or positive, perceptions of a project were felt by stakeholders external to the development process may influence the direction of drug development (Epstein, 1995, Bazell, 1998).

Low public or user support may be countered through process of interacting with the public through media channels, and user groups, promoting the drug. We define users at clinicians and patients. The media provides a good source for data in this area because it has been found to not only influence public opinion (and thereby indirectly influencing policy) (Holder and Treno, 1997) but also to influence firm decisions (Penna and Geels, 2012).

Furthermore, this is related to the influence of the media on innovation and the influence of stakeholders on the media (Lewenstein, 1995, Konrad, 2006). Here, while the media is recognised to influence the development trajectory of a project, this relationship is cyclical and involves the similar process of firms influencing the media. For instance, the media may be adopting and communicating the perception of the firm of the project rather than influencing this perception. This limitation to the use of the media as a proxy for stakeholder perception represents a complex relationship requiring careful assessment, demanding full credit to be given to the context of perceptions and the background of the stakeholders who hold them.

It is also relevant to discuss uncertainty in the perspectives taken by stakeholders. Here, a novel project will benefit from the influence of researchers promoting the approach, thereby having a big impact on stakeholder perception through the media and funders (Nuffield Council on Bioethics, 2012). Stakeholder perception, and particularly that of the users (patients and physicians), may also be influenced by the administration route of the drug or particularly unusual or severe side-effects (although it would be expected that severe adverse events would contribute towards a project being terminated for safety reasons).

In this section we have highlighted how stakeholders, external to the drug development process, can impact, both directly and indirectly, the progression of the innovation. It is therefore important to note that in this thesis there is an attempt to separate out the commercial expectations of project (as defined in the market demand construct), and other areas of expectations (technical, potential to address unmet need, etc.).



The influences highlighted in this section are most likely to contribute towards project drag, contributing towards an accumulation of concerns around drug development. Uniquely, compared to the other conditions identified in this thesis, stakeholder perspectives are likely to impact on a variety of departments within the organisation responsible for developing the drug.

#### **3.4.4 Organisational Environment**

The organisational environment that surrounds the innovation is not just important in terms of the type of organisation responsible for development, and its strategy, but also in terms of the influence that collaborative agreements exert on the progression of development.

Agreements between organisations can impact innovations on the project level, as well as internal organisational strategy influencing the project indirectly (Hill and Jones, 1999). The organisational strategy of the therapeutics portfolio (Pisano, 2006), and other projects influence decisions around a particular drug's development (Ahn et al., 2010). Specific issues addressed in the portfolio evaluation process, according to innovation management, include corporate objectives and strategies, relationships with existing markets, manufacturing, facility and equipment requirements (Tidd and Bessant, 2013).

With the reciprocal reliance demonstrated between large and small firms (Chapter 2), collaborative agreements and M&A events are likely to occur in most project lifecycles. Issues affecting the performance of innovations in the wake of collaborations or M&A include: similarities in firm culture, size, experience, and objectives (Pisano, 2006, Stuart et al., 2007, Lane and Lubatkin, 1998, Bstieler and Hemmert, 2010), and the facilitation of social capital formation through coordination, communication and interaction (Nahapiet and Ghoshal, 1998, Moran, 2005). We also observe that, in general M&A is detrimental to innovation progression (Hitt et al., 1991a, Ernst and Vitt, 2000, James, 2002)

Innovation projects in small firms are more vulnerable to the industrial dynamics that surround their organisation due to a tendency for a lack of resources in the UK (Hopkins et al., 2013). Industrial dynamics in this context refers to influences such as regulatory environments, access to funding or capabilities and changes in stock-price. Furthermore, the reliance of small firms, on collaborations, licenses and acquisitions, to progress their project to later stages of development, may lead to difficulties associated with integration and learning challenges, negatively affecting project.

In larger firms this influence is shielded due to the presence of routines, experience and financial independence. Indeed, cash resources are found to be significant in influencing decisions to continue projects from phase I to phase II trials. This was found by Guedj and Scharfstein (2004) who undertook a study showing that even early stage cash rich firms tended to take projects from phase I to phase II trials more readily than mature firms.

Firms are limited by their resources and capabilities, or those they can access, whereby larger firms would be expected to have a broader range available to them than smaller firms. In this, smaller firms have less strategic portfolio options than larger firms and therefore are expected to set lower thresholds (higher risk) contributing to project decision making.

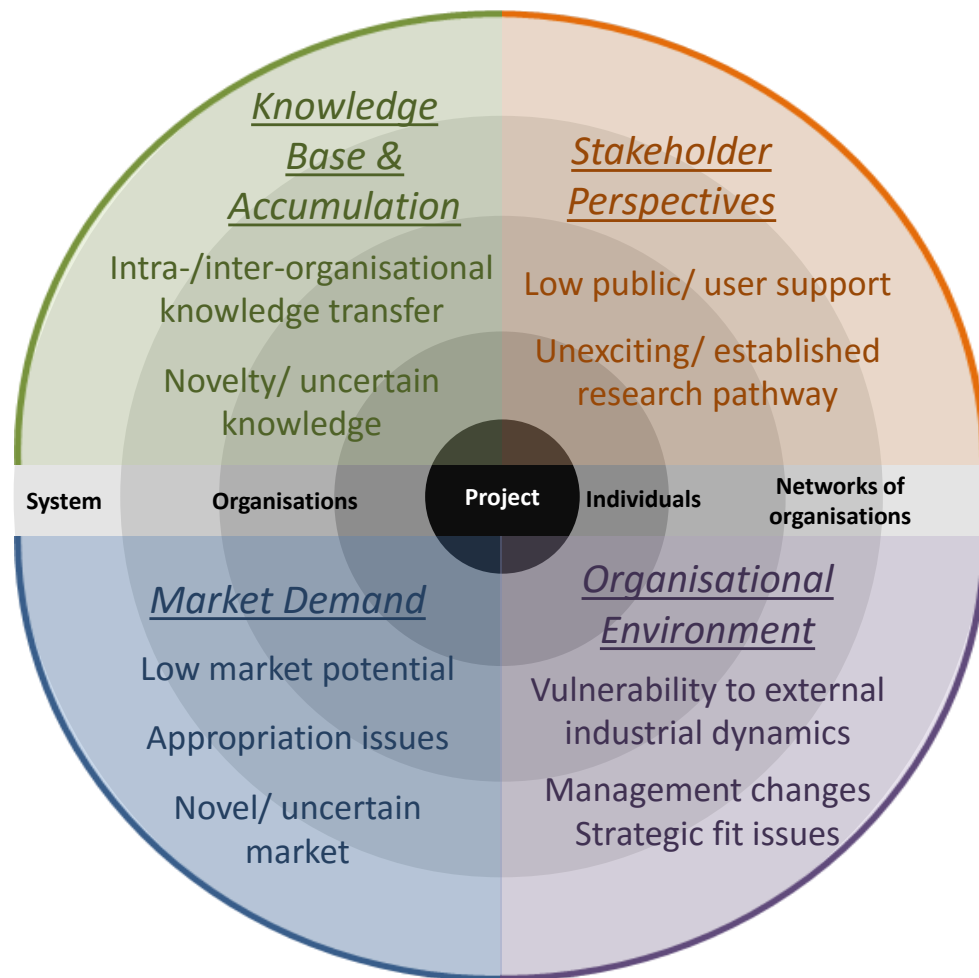
As the above discussion has relayed, it is clear that the organisational environment surrounding a firm will be a more salient issue in the case of smaller firms, as they are more vulnerable to industrial dynamics (e.g. access to funding, regulatory forces), and partnering relationships. Organisational environment would be anticipated to contribute to both project drag, in the interaction between a particular drug and other pipeline projects the organisation has, and go/no-go decisions, for instance where a merger or acquisition has occurred and the drug no longer shows strategic fit for the firm.

### **3.4.5 Summary and Framework Formation**

The purpose of this subsection has been to discuss the formulation of the framework which draws on the previously reviewed literature to categorise conditions and issues relevant to focus the case study research methodology (as will be discussed in Chapter 4). While identifying the four conditions (knowledge base and accumulation, market demand, stakeholder perspectives and organisational environment) this framework also maintains an appreciation for the multi-dimensional nature of the environment surrounding the progression of drug development. By combining these two considerations a framework is proposed as per Figure 3.

Although further operationalisation will be discussed in Chapter 4, in the first instance we take the issues highlighted in the previous sections, under the four condition headings, to indicate the direction of the investigation to come. This framework is used in the data collection and analysis of the case histories for this thesis, whereby each project's progression is discussed with consideration of all four conditions. In addition, we will draw on prior discussions of 'project drag' whereby issues discussed in terms of their role in gradually accumulating towards a project gaining or losing momentum.

We have also observed that each of the conditions may be situated in different departments within an organisation, for instance, knowledge accumulation would be located in the scientific research teams and market demand in the sales and marketing teams. It is therefore possible that while each condition is impacting the development outcome of the drug, there may be an influence of the decision making process found within the organisation, and its size, whereby the influence exerted by the departments involved disproportionately impact the effect of the condition at work.



**Figure 3 Framework for this thesis highlighting both the multi-dimensional nature of the internal and external environments influencing the development of a drug project, and the four conditions found to be most relevant for focusing the empirical case studies, including the suggested challenges to development within each category.**

### **3.5 Conclusion**

So far this thesis has discussed the empirical setting for this thesis, and characterised this historically in terms of paradigm shifts in drug development, industry strategy and

structure and approaches to oncology therapeutics. We built on this in the present Chapter by taking the development of biomedical technologies and projects from an innovation studies perspective. Here we have discussed the selection pressures directing innovation and contributing towards success or failure.

We first addressed this in line with the dimensional perspectives taken by many studies, in the influence of actors, organisations, individuals and networks. This discussion highlighted two gaps in the literature. Firstly, the need to focus on projects as the unit of analysis, thereby allowing for an appreciation of a holistic picture of drug development. Secondly, the lack of multidimensional approaches taken, whereby this thesis aims to incorporate issues on individual, organisational and network levels.

We have also assessed the literature in order to identify conditions influencing innovations, on these multiple levels. Here we demonstrated the significance of four conditions: knowledge base and accumulation, market demand, stakeholder perspectives and organisational environment. These conditions contributed towards the formulation of a framework which will be used in the empirical investigations for this thesis, namely in the construction and analysis of drug project case histories.

In the following Chapter we will discuss the method implemented to answer the research questions. This will involve discussion of the need for a multiple case study approach, incorporating in-depth investigation and systematic analysis to enable the thesis to fulfil the knowledge gaps identified in this literature review.

## 4 Research Design and Methods

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### 4.1 Research Design

This Chapter will discuss the process undertaken to collect and analyse data to address the research questions outlined in Chapter 1. Chapter 3 developed a multi-dimensional framework to study the influences on drug innovation, spanning organisational, individual and network perspectives. This literature review demonstrated an abundance of studies focusing within organisational boundaries, highlighting a need for a project-level approach to appreciate the multiplicity of organisations involved in drug development.

Following this observation, the thesis investigates 11 drug projects, and traces their progression through discovery and development. This enables an appreciation of the influences of the conditions identified in Chapter 3: knowledge base, market demand, stakeholder perspectives and organisational environment, have on drug progression.

In a similar approach to that of Blume (1992) the thesis employs an historical and cross-case study comparison of projects, comparing the trends in internal (knowledge, markets) and external (perspectives, environment) conditions from a multi-dimensional (network, organisational, and individual) approach. In addition, this thesis aims to draw out trends between cases, thereby informing a wider empirical context justifying the implementation of a multiple-case study comparative analysis.

Due to a lack of previous studies that have taken this type of approach, this methodology uses Eisenhardt's (1989) theory building procedure in order to extend existing knowledge, utilising the framework constructed in Chapter 3. As will become apparent in the following discussion, the strength of this approach is that it facilitates the construction of theories that are testable, and empirically valid.

We also consider, in the construction of this methodology, previous innovation studies, most significantly the SAPPHO report, which similarly focuses on product innovation as the unit of analysis and analyses multiple cases (Rothwell et al., 1974). The method used in the SAPPHO study emphasised pairwise comparisons between successes and failures, in the context of predetermined multiple factors. Reflecting on this, and the ambition of this thesis, in understanding the conditions impacting innovations, Eisenhardt's (1989) roadmap is complemented, in this method, by Yin's (2009), multiple case study approach, and Ragin's (1987) Qualitative Case Analysis (QCA).

#### **4.1.1 Suitability of Multiple Case Study/QCA for Understanding Drug Innovation**

The implementation of multiple case studies and a QCA is further justified by the limitations associated with small N case study (qualitative research) methods and variable-based (quantitative research) methods.

Small-N research allows cases to be considered using many variables to explain observed outcomes. This involves research strategies that gain a deep understanding of a topic, but lack breadth (Ragin, 2000:22). With a small number of cases, there is a danger of attributing inferences, where any shared characteristic is interpreted as a cause (Geddes, 2003). Furthermore, it may be difficult to ascertain policy-relevant conclusions which account for alternative, context-dependent outcomes.

A multiple, medium N approach overcomes these issues enabling a degree of generalisation to be made while accounting for a variety of scenarios retaining the detail and exploratory power garnered from case studies. This is one of the main motivators for the method presented in this Chapter.

As the etymology of the word implies, 'quantitative' research methods are concerned with data of high quantity, while sacrificing detailed understandings of the cases studied. Here, a large number of cases are analysed using a small number of variables, with an emphasis placed on breadth of insights, as opposed to depth (Ragin, 2000:22). However, where inferences regarding causation are taken from single instances of co-occurrence, quantitative research has been accused of too often inferring causation and over-generalisation (Geddes, 2003).

Further reasons against using a quantitative approach are: 1) the issue of correlations between independent variables (endogeneity) and the frequent occurrence of this in reality (Ragin, 2008:180); 2) the reliance of conclusions based on net effects and therefore the need for strong model specification (Ragin, 2008:157-158, 176-179); 3) the unrealistic representation of reality as symmetric associations (Ragin, 2008:3, Berg-Schlosser et al., 2009:8-9); 4) the representation of causal factors as permanently causal (Berg-Schlosser et al., 2009:8-9); 5) the difficulty of representing data as linear (Berg-Schlosser et al., 2009:8-9, Yamasaki and Rihoux, 2009:141); 6) the often mechanistic application (Yamasaki and Rihoux, 2009:142); 7) the independent influence that variables have on the outcome with difficulty in consideration of context and interdependencies (Ragin, 2008:112, Berg-Schlosser et al., 2009:8-9); and 8) the influence that a reliance on correlations has on the conflation of results (Ragin, 2008).

These factors, along with the justifications laid out below, have influenced the decision to pursue an approach based on QCA, which overcomes many of these issues. In particular, in this study we are interested in drug development, occurring over 10-20 years, implying a high chance that variables are interdependent and influence outcomes in a variety of ways.

## **4.2 Justification for Multiple Case Study Approach**

The benefits of multiple case studies, particularly in overcoming the aforementioned concerns with small N case study and large N quantitative research designs, are highlighted in this section. This provides further justification for the implementation of a multiple case study approach, with particular attention paid to the QCA methodology.

### **4.2.1 'Objectivity'**

One critique of case studies is the lack of objectivity in the view of the cases in question (Flyvbjerg, 2006). One response to this is that all methods can be interpreted to have an element of subjectivity (ibid). For instance, in quantitative research variable definition, the data used and the extent to which this is an indicator of the phenomena to be explained, are reliant on the researcher's view of the world.

In QCA there is a theoretical basis for initial concept formation, and scoring (calibration) of cases indicating set (factor/condition) membership should be explicitly given in the presentation of the method (see section 4.4.1.2 below) (Smithson and Verkuilen, 2006:18). In contrast, quantitative statistical research methods, tend not to clearly discuss decisions such as variable bounding and inclusion criteria. In this way, QCA has been described as uncovering the equivalent 'black box' in quantitative research, where data is modelled and the 'answer' is seemingly mechanically arrived at (Berg-Schlosser et al., 2009:14).

In addition, and further related to this issue of objectivity vs. subjectivity is the ability for case study research approaches to appreciate the world as a social construction of reality, whereby the interpretive flexibility of categories and cases are recognised (Pinch and Bijker, 1984). Furthermore, case study approaches (e.g. QCA) provides a strategy accounting for the complex and context-dependent nature of reality.

### **4.2.2 Interpretability**

Case study research methods, such as QCA, allow for a proximity in the relationship between the data and analysis. This is less apparent in regression analysis which takes a more detached approach. The discussion of interpretability naturally relates to the previous consideration of objectivity where a close relationship between data and

analysis might be deemed to be a negative characteristic of the research design. However, the inherent benefits of a are in where the output of the analysis<sup>50</sup> facilitating interpretation, not only providing a realistic perspective of the empirical case, but also implying clear and concise theoretical implications (Berg-Schlosser et al., 2009:6).

#### **4.2.3 Data Sources**

Another advantage of the case study approach, particularly in the context of this thesis is the possibility to combine data from a diverse range of sources. This is particularly important when there are not relevant predefined databases, as is the case in this research. Furthermore, by implementing a QCA, insights can be garnered from both qualitative and quantitative sources, and combined to formulate a score (Berg-Schlosser et al., 2009:13). This is particularly important when considering the suitability of different types of indicators in their attempt to represent a socially complex phenomenon.

#### **4.2.4 Causality**

Whilst regression allows for inference of causality based on covariance and association, case studies provide a detailed examination of the mechanisms at work. The descriptive analysis implemented in this research facilitates causal analysis through a process of identifying patterns, trends, similarities and differences, with an iterative examination of the literature providing explanatory power. A QCA provides an assessment of causal connections through the determination of necessary and sufficient conditions for observed outcomes (Ragin, 2008:20). Furthermore the ability for a QCA to examine asymmetrical relationships, i.e. different determinants of opposing outcomes, enables a more accurate representation of the world, as opposed to the symmetric covariations arising from correlational techniques (Ragin, 2008:15).

#### **4.2.5 Equifinality and Multifinality**

The final argument supporting use of a case study approach, and most significantly in the application of a QCA, is that the conclusions arising represent multiple conjunctural causation, which is particularly important in the context of uncertainty as is seen in innovation (Berg-Schlosser et al., 2009:8-9). Specifically, multiple conjunctural causation may include situations of equifinality, the combination of different pathways (combinations of factors/conditions) which lead to the same outcome, and multifinality, one condition (or combination of conditions) may combine to produce two different

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<sup>50</sup> As will be discussed in the following sections the main output of a QCA is a solution representing the configuration of conditions contributing towards the outcome.



outcomes (Schneider and Wagemann, 2012:5-6). These potentialities in the output of QCA mean that the conclusions drawn represent an accurate picture of the complex situations that make up a social phenomenon. The appreciation of multiple conjunctural causality is significant in policy-oriented research, where there is an emphasis on understanding how an outcome is influenced and the context-dependent nature of the causal conditions leading to particular outcomes (Ragin, 2008:182)

### **4.3 QCA History and Logic**

Section 4.4 of this Chapter, will describe Eisenhardt's roadmap, alongside a discussion of how a QCA is undertaken. However, in order to contextualise this discussion, it is necessary to provide some background on QCA, as this is a relatively new method for innovation studies.

Ragin (1987:1) suggests that comparative methods, such as QCA epitomise 'virtually all empirical social research' due to the overarching focus of comparisons in social inquiry. Despite QCA providing a middle ground between qualitative and quantitative methods, the logic behind QCA shows a stronger affiliation with the former (Ragin, 2000, Ragin, 2008, Berg-Schlosser et al., 2009). Specifically, qualitative approaches and QCA both centre on the identification of consistent connections and analytic induction, i.e. the identification of trends from empirical instances (Ragin, 2008:2).

QCA is a Configurational Comparative Method, and as such, utilises set theory and Boolean algebra to analyse cases according to configurations of characteristics (conditions) (Rihoux and Ragin, 2009).

#### **4.3.1 Set Relations and Boolean Algebra**

Set theory is one of the fundamental components of QCA and centres on the idea that cases can be categorised into the 'set', or conditions, they fall into. The use of set relations is frequently apparent in the language used in theoretical discourse (Berg-Schlosser et al., 2009:6). For instance, the phrase 'the UK is a democracy' is a set relation whereby the 'UK' belongs to the subset of cases defined by the condition 'democracies'.

This subset and superset relationship between cases and conditions (sets) also provides the basis for distinguishing necessary and sufficient conditions. In this, necessary conditions are conditions (sets) which are present whenever the outcome is present ('Y' (the outcome) is a subset of 'X' (the condition)) (Schneider and Wagemann, 2012:69-70). Similarly, a sufficient condition is defined when the presence of the condition is a subset of the presence of the outcome. Here, whenever the condition is present the

outcome may be present but there are also instances when the outcome is present where the condition is not (Schneider and Wagemann, 2012:57).

In operationalising the logic of set theory, QCA employs Boolean algebra to represent set relations. Boolean algebra relies on the classification of conditions as true (or present) and false (or absent) and the analysis of a range of conditions using the application of basic operators, including: 'intersection'/multiplication (or logical AND), 'union'/addition (or logical OR) and 'negation' (or logical NOT) (Smithson and Verkuilen, 2006:4-6). Boolean operators are not arithmetic; rather they rely on a set of rules for simplification and minimisation (discussed in section 4.4.3.1.2.3) (Schneider and Wagemann, 2012:104-106). One of the main benefits of Boolean algebra is its logic enabling instances to be defined in terms of the conditions that categorise them, in conjunctions and disjunctions, (Ragin, 1987:13-15). This maximises use of the data available, where both absent and present conditions contribute towards the output<sup>51</sup> (ibid).

The method of QCA employed in this thesis is crisp set QCA (csQCA) which relies on a dichotomised coding system limiting the level of set membership to either full membership (1), or full non-membership (0). This simple codification, which is used to determine whether conditions and outcomes are present or absent, has been critiqued due to the lack of appreciation for social reality in the partial membership of cases into sets. The alternative is fuzzy set QCA (fsQCA) in which cases can be scored in accordance with partial membership indicated by values assigned between 0 and 1. This method is usually preferred due to the increased degree of detail it enables, where csQCA is seen to be unrepresentative of reality due to its simplicity. However, in this thesis, due to the lack of agreed standards to facilitate discrete calibration<sup>52</sup>, it is difficult to define degrees of difference and therefore assign definite scores representing partial membership, therefore a csQCA is preferable. Furthermore, in fsQCA it is necessary for all conditions, including the outcome to be represented on a scale from 0 to 1, which would not be possible with success, using the definition employed in this thesis.

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<sup>51</sup> Note the distinction used in this thesis between output, used to signify the solution generated from the analysis of sufficient conditions, and/or the necessary nature of condition(s); and outcome (Y), used to describe whether a project was successful (presence of the outcome) or unsuccessful (absence of the outcome).

<sup>52</sup> Calibration is a process by which a fuzzy-set, or crisp-set score is assigned in line with externally determined, and accepted thresholds, for more explanation of this see Section 4.4.3.1

#### 4.4 Eisenhardt's Roadmap

As mentioned above, this thesis follows Eisenhardt's roadmap of eight steps for developing and building theory, while introducing good practice in case studies, as suggested by Yin (2009), and Ragin's (1987) QCA. Despite the apparent linearity (Table 4) of Eisenhardt's approach, the constitutive steps should be viewed as incorporating feedback loops. This section will outline steps and further describe the implementation of each in this thesis.

Step	Activity
1. <u>Getting Started</u>	Definition of research question Possibly a priori constructs
2. <u>Selecting Cases</u>	Neither theory nor hypotheses Specified population Theoretical, not random sampling
3. <u>Crafting Instruments and Protocols</u>	Multiple data collection method Qualitative and quantitative data combined Multiple investigators
4. <u>Entering the Field</u>	Overlap data collection and analysis including field notes Flexible and opportunistic data collection methods
5. <u>Analysing Data</u>	Within-case analysis Cross-case pattern search using divergent techniques
6. <u>Shaping Hypotheses</u>	Iterative tabulation of evidence for each construct Replication, not sampling, logic across cases
7. <u>Enfolding Literature</u>	Comparison with conflicting literature Comparison with similar literature
8. <u>Reaching Closure</u>	Theoretical saturation when possible

**Table 4 Reproduction of Table 1 from Eisenhardt (1989) - Process of Building Theory from Case Study Research summarising the progression of Eisenhardt's roadmap.**

##### 4.4.1 Step 1 – Getting Started

Step one in Eisenhardt's roadmap is for the researcher to embed themselves in the research question and to define a particular research focus<sup>53</sup> (Eisenhardt, 1989:536). This involves the determination of constructs from existing theory, enabling the researcher to focus the data collection stages with consideration of the measurement of these pre-defined constructs. However, Eisenhardt introduces the first, of many iterative

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<sup>53</sup> This embeddedness, according to Eisenhardt, is observed to be particularly beneficial when it comes to digesting, analysing and drawing conclusions from the data collected, otherwise, she states 'it is easy to become overwhelmed by the volume of data' (Eisenhardt, 1989:536).

processes here, where this definition and identification of constructs should remain tentative and flexible to adaptation.

This emphasis, on the formulation of constructs, echoes aspects highlighted by both Yin (2009) and Ragin (Ragin, 2000). Yin (2009), defines construct validity as key to producing quality case study analysis, thereby supporting the importance of construct formulation. For QCA, constructs are akin to conditions, formulated by drawing on existing knowledge, and brought together to product a framework. Furthermore, the use of existing theory, as highlighted by Eisenhardt (1989), is of central importance in the calibration of conditions in a QCA (Ragin, 2000).

Furthermore, in QCA, theory plays an important role in defining relevant cases and resolving limited diversity in assigning counterfactuals in truth table analysis (section 4.4) and in interpreting results (Berg-Schlosser et al., 2009:7).

Thorough assessment of theoretical contributions is of central importance when considering that different theories may not necessarily be competing but may complement each other (Ragin, 2008:179). Therefore, in QCA, there is an emphasis on the researchers' theoretical and substantive knowledge of both the topic and the cases in question (Berg-Schlosser et al., 2009:12).

#### 4.4.1.1 Step 1 Implemented

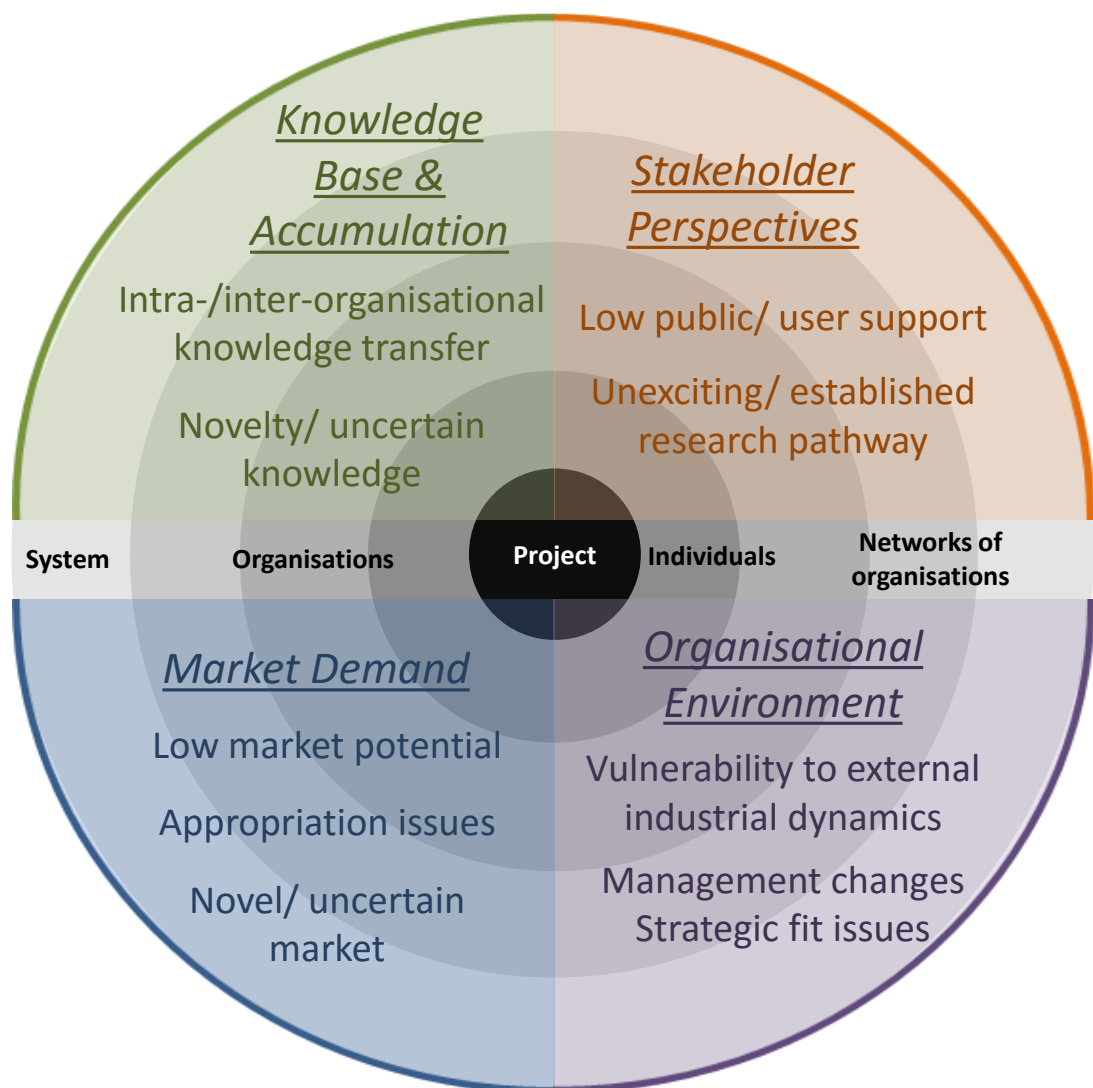
The implementation of step one has been illustrated in the formulation and development of the research questions and framework (in Chapters 2 and 3). The resulting framework was formulated both in order to facilitate the collection of data, and to inform that analysis of that data in the descriptive analysis.

Issues highlighted in the framework development (Figure 4) fit into Eisenhardt's roadmap by providing the contextual questions that guide an exploration of the potential solutions (theories) contributing towards distinguishing successful, from unsuccessful, projects. It is these issues that are explicitly discussed in the case histories that follow in Chapters 6 and 7.

#### 4.4.1.2 Operationalisation of the Framework

This section outlines the operationalisation of the framework (Figure 4) both for the descriptive analysis (how conditions have been measured using the data sources) and the QCA (scoring of presence and absence of a condition). One of the key contributions of this thesis is in the formulation and operationalisation of the framework, where novel proxy measures account for the conditions identified.

For the QCA calibration (scoring the membership of a case to each set/condition) the default position is 0 rather than 1, i.e. the condition is absent unless its presence can be proved. In other words, the scoring of the '0' in QCA does not necessarily represent the opposite of the condition, e.g. 'low market demand' but merely the absence of the condition, or the absence of 'high market demand' in this case. This is a key consideration in contextualising the scoring for the QCA as represented in the section subheading under each case in Chapters 6 and 7.



**Figure 4 Framework as developed in Chapter3**

#### 4.4.1.2.1 *Knowledge Base and Accumulation (represented as 'B' in QCA)*

In order to capture both the knowledge base and level of knowledge accumulation it is necessary to look at the novelty of a particular scientific and technological approach, and thereby the level of knowledge supporting the initial discovery and development of the drug, and the extent to which knowledge transfer is facilitated between individuals involved in the process.

As a starting point we explore the technological approach used as a basis for the development of the drug, for instance, kinase inhibitors, and/or mabs. Secondly, we consider the progression and results from the trials contributing towards drug development.

To capture a picture of the accumulation of knowledge throughout the development of the project we firstly assume that for a project that has remained in the same organisation throughout its life-cycle, the knowledge transfer between teams would be efficient due to the development of routines in experienced teams (Nelson and Winter, 1982). We infer that when the composition of the research groups changes (upon license acquisitions, mergers and acquisitions and during alliances) there is the potential for negative implications for the transfer of knowledge. From the literature explored in Chapter 3 we can assume that with the action of a consistent research group the progress of a project would be benefited through the establishment of shared visions which in turn facilitates knowledge transfer. However, the introduction of new skills previously lacking in a research group may necessitate collaborative relationships to be established, thereby benefiting the innovation process.

The knowledge base was further determined by consideration of the novelty of the technological area implemented, and the duration of the existence of the scientific knowledge base forming the basis for the drug's development. In addition, for targeted therapies, target validation was also considered; whereby if a drug with the same target had been previously approved the target was deemed to be validated.

#### 4.4.1.2.2 *Market Demand (represented as 'D' in QCA)*

The framework (Figure 4) highlights the issues within the market demand conditions: (i) low market potential (ii) appropriability issues and (iii) novel/uncertain markets.

The first factor taken into consideration in contributing towards market potential is the number of indications for which the project was being developed. Indications were only included if clinical development was being progressed (realised potential) and not if it was merely stated that the drug may be more widely applicable in the future (expected

potential). However, this is not unproblematic because a realised potential is more feasible for projects developed by big pharma with abundant resources, as opposed to smaller firms. However, it is the most accurate way of gaining an idea of market potential, overcoming the issue that a firm may claim broad applications that are unrealistic.

Media and press reports of expected market demand were also taken into account in a drugs' market potential. Orphan drug status was considered under the umbrella of market demand, whereby low expected market size would be partially mitigated by the promise of greater exclusivity and lower development costs.

In addition, the level of competition, in terms of standard of care for the primary indication, was also considered. If the disease was previously untreated it would be expected that, even if a small patient population was represented, the drug could command a high price and would be easier to get approved. However, pricing is controversial and does not necessarily provide a guarantee of revenues; therefore, this thesis does not place significant emphasis on pricing expectations under the umbrella of potential market demand.

Appropriability issues are accounted for through capturing a picture of the duration of patent protection remaining for the drug. This is relevant because if protection is near expiry it is assumed that the project no longer has high commercial attraction for a potential investor or developing firm. Patent protection is also considered in the context of the stage of project development, with data on average clinical trial durations considered.

The novelty/uncertainty of the market is partially linked to the approach used in developing the drug and whether that particular approach has been used previously. If there is no instance of the approach being used previously it is assumed that the drug will suffer from the uncertainty surrounding its market potential.

#### 4.4.1.2.3 *Stakeholder Perspective (represented as 'S' in QCA)*

Stakeholder perspectives were considered with data from press and media reports. While it is clear that this perception is influenced by the firms involved in drug development media reports captures the views of stakeholders, which in turn is hypothesised to feed back into firm's decisions around project development. In addition, interviews presented a perspective of the expectations felt by those in the development of the drug. The media is a key source indicator for this condition, justified through the observation that researchers act to promote technologies by communicating with the media, funders and the public (Nuffield Council on Bioethics, 2012).

Data included in media reports range from describing drugs as highly promising, to not mentioning the drug project at all. The latter scenario was taken to imply a general lack of enthusiasm for the project, both from the developing firm (i.e. releasing no press releases concerning the development of the drug), and analysts. These reports were taken to imply the general perspectives of stakeholders (outside the developing organisation) about the project. In addition, in some cases it is also relevant to look at particularly difficult administration routes, and/or unusual side effects that may have an influence on users (physicians and/or patients) perspectives. For instance, patient preference prioritises the oral administration of drugs (Borner et al., 2001).

In addition, we infer that if a project is part of a long established research pathway, that it will be relatively unexciting and therefore will receive a less enthusiastic reception from stakeholders. This is the case where a drug is being developed as a cytotoxin, for instance, whereby it would not receive the benefits from being 'pioneering'.

#### 4.4.1.2.4 *Organisational Environment (represented as 'E' in QCA)*

The issues suggested to be challenging for drug projects under the umbrella of organisational environment include: 1) vulnerabilities to external industry dynamics, 2) management changes and 3) issues relating to the project's strategic fit within the host organisation.

The first of these difficulties of firms in terms of industrial dynamics, is relatively straight forward to assess whereby firms suffering from funding issues, regulatory issues or mergers and acquisitions would be expected to have external disruptions that would cause problems for their pipeline. Disruptions may include delays in gaining regulatory approval for trials, having a cash burn rate that is not sustainable for their host organisation, running out of money, employee redundancies relating to M&A events or the moving of premises following a merger or acquisition. Related to this is the idea that changes in management structures, usually (but not exclusively) cause by mergers and acquisitions or licensing agreements, may also have detrimental effects on the development of the project in terms of re-opening debates about the priority, or direction of a project's development.

In addition, strategic fit issues were also considered. These were judged to be present where the project was found to show a level of discord with the firm's reported strategy.



#### 4.4.1.2.5 *Outcome – Success:*

As suggested at previously in the Chapter, the outcome of each project was determined by approval (i.e. success) by a regulatory agency, or discontinuation/termination, or no-development reported (as per Pharmaprojects) (unsuccessful).

### 4.4.2 Steps 2 and 3 – Selecting Cases and Crafting Instruments and Protocols

The second step is the selection of cases, where the concept of a ‘population’ becomes important because it provides a foundation for the selection of cases based on the control of less relevant variation between cases, and providing a boundary to the generalisability of the research findings (Eisenhardt, 1989). The third step closely follows and asserts the ‘Crafting Instruments and Protocols’. In this step the research must identify the sources of data and outline the data collection methods. Eisenhardt (1989) emphasises that theory-building approaches generally require the collection of data from multiple sources, using multiple methods, an approach also followed by Yin (2009) in his discussion of good practice in case study design.

It is in this step that triangulation becomes an important step allowing for ‘stronger substantiation of constructs and hypotheses’ (Eisenhardt, 1989:538, Yin, 2009). These methods may involve breaking away from the traditional assumption that case study analysis involves the collection of qualitative data, as opposed to quantitative data. These approaches are complementary, where quantitative research may indicate an overarching pattern, qualitative data allows for a detailed understanding of the reasoning behind a particular relationship.

#### 4.4.2.1 Steps 2 and 3 Implemented

The implementation of steps two and three in this study involve the selection of cases and an exploration into the data sources used in order to construct the case histories that provide the basis for the analysis in steps 4 and 5.

#### 4.4.2.2 Case Selection

There were six main criteria were used to define the sample of drug projects in this research project. These were implemented to bound the project to facilitate research that was both in-depth and broadly applicable. The case selection here allows us to talk about the dataset as a ‘population’ of drugs aimed at a rare cancer, approved or discontinued (post-phase II) between 1999 and 2011, that had some involvement from a UK company, although clearly the dataset is a sample of all rare cancer drugs, cancer drugs and orphan drugs developed globally.

In this research a 'project' is the unit of analysis and is defined as a drug which can be traced from discovery and through development. Although discussions may include precursor drugs, i.e. drugs that contributed towards the development of the index drug, it will not extend to other drugs in the same programme of research (e.g. multiple compounds against the same target).

This thesis fundamentally focused on rare cancers in an attempt to pre-empt some of the issues that will arise in the wake of personalised medicine, an increasingly popular approach to treatments. This shift implies that new business models, strategies and policies may need to be introduced, which will rely on a deeper understanding of the dynamics of drug innovation in diseases that affect small populations.

#### 4.4.2.2.1 *UK-based*

The project must have had some involvement from a UK company (i.e. a company with a UK HQ). In some cases, this includes research carried out in a different country. For instance, GSK is a UK company and has projects included in the dataset despite a large majority of their oncology programmes being located in the USA during the time period this thesis is concerned with. Projects and companies were identified using the Pharmaprojects<sup>54</sup> industry database (also used in Hopkins et al., 2013, Abrantes-Metz et al., 2004, Chandy et al., 2006, Mullen et al., 1997).

The UK focus was chosen due to the amount of data on firm activity that is publicly available and therefore relatively accessible (given that firms in the industry can be secretive (Goldacre, 2012)). Related to this it was also felt that for fieldwork interviews (see section below 4.3.2) identifying and undertaking conversations with individuals in the UK would be more straightforward.

#### 4.4.2.2.2 *Life Cycle Completion Post-Phase II*

In keeping with project SAPPHO-inspired (Rothwell et al., 1974, Rothwell, 1992) method, and QCA, cases were required to represent both successful and failed outcomes. This is important as it provides a balanced view of the case study analysis and is not skewed towards representing success stories thereby avoiding survivor bias.

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<sup>54</sup> In addition to being widely used by scholarly articles, Pharmaprojects is also an accepted industry database. In 1997 it was rated to be 'probably the most systematic and widely used information sources' with the widest coverage (Mullen, 1997). Currently Pharmaprojects provides access to over 60,000 detailed drug profiles providing information such as development history timelines, licensing information, clinical trials, and molecular structure ([www.citeline.com/products/pharmaprojects](http://www.citeline.com/products/pharmaprojects) )

In order to include case studies with different outcomes it was first necessary to define what was meant by success and failure. In the context of this thesis the ambition of is to investigate the innovative process during clinical development of the drug. Therefore, it is relevant to define a 'successful' drug project as one which achieved approval by a regulatory agency in either Europe or the USA, the two major markets targeted by UK firms<sup>55</sup> (IMS Institute for Healthcare Informatics, 2012).

Failure was defined as occurring when drug projects had been discontinued for non-technical reasons in development post-initiation of phase II trials, but not where development was discontinued for safety or severe efficacy reasons.

There are several facets of this definition. Firstly, interest in drug projects discontinued for non-technical reasons is of relevance due to the idea that there is no policy, management, or industrial action that could change such an outcome. In addition, a 'severe' lack of efficacy, i.e. where trials showed no responses in patients, was also deemed to be due to the scientific grounding of a project thereby proving irrelevant in a policy context. This is a difficult measure because sufficient efficacy is subjective, where enough efficacy to justify continuation of a project differs in accordance with the decision maker. The second aspect of the definition of a 'failed' project is in the prior initiation of a phase II trial. This distinction is warranted because drugs more often fail phase I studies for safety reasons, and projects abandoned at an early stage may not have been subject of substantial investment, or interest, internal or external to the host organisation, making the constructing a case history more problematic.

#### 4.4.2.2.3 *Time Period*

It was decided that a time period of 1999-2011 for a project to complete its life cycle (i.e. either be discontinued or approved) would be suitable in order to provide a time period balancing an appreciation of recency whereby only contemporary approaches to drug discovery and development are relevant, while obtaining a case study population with internal comparability. Furthermore, data for projects developed earlier than the 1990s would be harder to access and gather.

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<sup>55</sup> In 2006 EU5 (France, Germany, Italy, Spain and UK) and USA accounted for 19% and 41%, respectively, (60% total) of the global spending on medicines, according to an IMS Institute for Healthcare Informatics report). In 2011 this was reduced to 51% total combined, mainly due to rising markets in emerging economies (e.g. Russia, Brazil, China etc.) (IMS Institute for Healthcare Informatics,

#### 4.4.2.2.4 Defining 'Rare'

A rare cancer was defined as being orphan in both the USA and Europe, which are, as noted above, the major markets for UK firms. Due to the differences in how each region defines 'orphan' (see discussion in Chapter 5 regarding the Orphan Drug legislation) and the variations seen in how prevalence and incidence is measures, in terms of how different types of cancers are defined, i.e. grouped together or split, 'rare' status was defined from the USA database at [www.rarediseases.info.nih.gov](http://www.rarediseases.info.nih.gov), and in Europe, the [www.orpha.net](http://www.orpha.net) database. The resulting types of cancer for inclusion are shown in Table 5.

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Cancer, brain
Cancer, gastrointestinal, stomach
Cancer, oesophageal
Cancer, pancreatic
Cancer, nasopharyngeal
Cancer, leukaemia, hairy cell
Cancer, leukaemia, acute lymphocytic
Cancer, leukaemia, acute myelogenous
Cancer, leukaemia, chronic lymphocytic
Cancer, leukaemia, chronic myelogenous
Cancer, lung, small cell
Cancer, lymphoma, Hodgkin`s
Cancer, mesothelioma
Cancer, neuroendocrine, carcinoid
Cancer, neuroendocrine, neuroblastoma
Cancer, sarcoma, Ewing`s
Cancer, sarcoma, Kaposi`s
Cancer, sarcoma, lipo
Cancer, sarcoma, osteo
Cancer, sarcoma, soft tissue
Cancer, gastrointestinal, stromal

**Table 5 Relevant primary indications (as defined by Pharmaprojects). 'Rare' status defined as rare in Europe ([www.orpha.net](http://www.orpha.net)) and USA ([www.rarediseases.info.nih.gov](http://www.rarediseases.info.nih.gov))**

#### 4.4.2.2.5 Pharmaprojects Primary Indication

The projects identified for inclusion into this study must have been described by Pharmaprojects as having had a rare cancer as their primary indication, to control for situations where the drug has been approved initially for a more common condition and then approved for secondary indications.

In instances where the drug was indicated for cancer in general and specified down to a rare cancer at a later date, such as was the case with plevitrexed, then the case was included. This was in contrast to where a drug was indicated for a non-rare cancer, where the initial research stream was discontinued and development was picked up in a rare cancer, where cases would have been excluded from the dataset.

Furthermore, due to the potential for a drug to be developed for multiple indications, some included projects did show a high market potential. The justification for inclusion of these instances was that the rare cancer was the primary indication and so projects developed in a scenario of multiple indications are still contributing towards the overall population of drugs for rare cancers (and diseases).

#### 4.4.2.2.6 *Relevant Therapy Type*

In order to ensure that the drug projects captured were relevant and presented novel approaches to cancer therapy, i.e. the dataset was not to include 'me-too' drugs, generics, or combinations of existing therapies, the Pharmaprojects classification for 'Primary Therapy' was used as a filter with relevant therapy types including gene therapies, haematological etc. (for full list see Table 6).

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Anticancer  
 Antisense therapy  
 Cytokine  
 Gene therapy  
 Haematological  
 Hormone  
 Immunoconjugate  
 Immunoglobulin  
 Immunological  
 Immunomodulator  
 Immunostimulant  
 Immunosuppressant  
 Immunotoxin  
 Monoclonal antibody  
 Neurological  
 Oligonucleotide  
 Otological  
 Prostaglandin  
 Recombinant  
 Recombinant growth factor  
 Recombinant hormone  
 Recombinant interferon  
 Recombinant interleukin  
 Recombinant vaccine

Releasing hormone  
 Somatostatin  
 Stomatological  
 Therapeutic vaccine

**Table 6 Relevant (included) primary therapy description (as defined by Pharmaprojects)**

#### 4.4.2.3 Data Sources

Data was collected from publicly available sources and some interviews were also carried out. A detailed picture of the case was constructed prior to interviews. This allowed interviewees to comment on the case history, identify gaps or highlight controversial points. These sources are complementary, with the necessity of gathering documentary evidence stemming from the issue of recall in interviewing individuals regarding events that occurred around 10-20 years ago, and the potential for individuals to present an unbalanced view of the development of a project.

##### 4.4.2.3.1 *Publicly Available Sources*

Data sources that were considered 'publicly available'<sup>56</sup> included: newspaper and press reports, websites (including, but not limited to EURORDIS - [www.eurodis.com](http://www.eurodis.com), [www.orphan.net](http://www.orphan.net), [www.dailymed.nlm.nih.gov/dailymed](http://www.dailymed.nlm.nih.gov/dailymed), [www.cancer.gov](http://www.cancer.gov), [www.nice.org.uk](http://www.nice.org.uk), [www.druginfo.nlm.nih.gov/drugportal](http://www.druginfo.nlm.nih.gov/drugportal), [www.accessdata.fda.gov/scripts/cder/drugsatfda](http://www.accessdata.fda.gov/scripts/cder/drugsatfda), as well as company websites), press releases, firm annual reports, industry analytics/observers, scientific publications (identified through PubMed, Scopus and/or Web of Science).

The construction of the case histories held media reports as an important and informative source of data. These channels are used strategically to promote social issues (Holder and Treno, 1997), mobilise resources (Nahuis and Boon, 2011) and effect change (Balasegaram et al., 2008). Therefore, media reports are a relevant source with consideration of the study's aim, to capture the perceptions and expectations of individuals and organisations at different times during the life cycle of a project. Media reports were found through the Nexis database ([www.nexis.com](http://www.nexis.com)).

Data collection was focused by the framework developed from the literature review (initially around the four broad factors and later, to specifically answer the identified issues from the development of the framework). The collection of data and construction

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<sup>56</sup> Some were access on a subscription basis (most widely through University subscriptions)

of the case histories was initially chronological but also took on a factor/condition structure.

#### 4.4.2.3.2 Interviews

A total of 9 out of 11 cases were covered with at least one type of correspondence with scientists, and/or industry stakeholders, involved in the development of that project (Table 7). Interestingly there is no trend towards interviewees willing to discuss project development for successful projects over failures, whereby we see no interviewees for pazopanib (success) or Prolarix (failure), and only email correspondence for two other successes (nelarabine and temozolomide).

Case	Interview undertaken?	Type of correspondence (number of individuals)	Case history validated by interviewees
<b>Pazopanib</b>	N	-	-
<b>Nelarabine</b>	Y	Email correspondence (1)	Yes
<b>Barasertib</b>	Y	Interview (1)	No
<b>Plevitrexed</b>	Y	Interview (1)	Yes
<b>Temozolomide</b>	Y	Email correspondence (1)	Yes
<b>Campath</b>	Y	Interview (3)	Yes
<b>Gemtuzumab</b>	Y	Interview (2)	No
<b>Banoxantrone</b>	Y	Interview (1); Email correspondence (1)	Yes
<b>TransMID</b>	Y	Interview (2)	Yes
<b>Prolarix</b>	N	-	-
<b>CAT3888</b>	Y	Interview (1)	No

**Table 7 Summary of the interviews undertaken for each of the projects investigated in this research project**

Despite an appreciation that these interviews provided an additional layer of detail about the environment surrounding the projects in question, there were issues associated with access to willing participants. A total of 54 approaches were made, with multiple emails being sent to each individual (response rate of just over 1 in 3). In addition, 9 key individuals were re-sent emails including the completed case history review for comment (2 of the email correspondences mentioned above resulted from this).

Access issues were, in part, associated with the identification of individuals involved in key stages of development of a project, particularly in the opaque structure of a large firm, for instance in identifying individuals involved in, e.g. pazopanib, developed by GSK. Furthermore, of the individuals contacted some raised confidentiality concerns in relation to talking about even historical projects.

In order to attempt to counter these concerns, interviewees were given the choice of whether they wished to remain anonymous, to be named in association with the project they were interviewed for (see Appendix 1 for a list of interviewees), or even just to comment on, or confirm the information already in the public domain. Blanket anonymisation was not implemented as, in some cases, it was useful to contextualise the informant by their involvement in the drug project.

Informants were supplied with an information sheet and consent form, which they were asked to sign, prior to the interview<sup>57</sup>. The research was approved through the University's ethical review board, and interviews were conducted in line with the relevant guidelines.

Interviews were semi-structured, and focused on ascertaining the interviewee's perspective and perception of the project in question. There was also effort made to fill some factual gaps in the chronological and contextual narrative surrounding the drug project. In addition to the interviews carried out aimed at specific projects an additional 3 interviews were undertaken with a more general theme, taking the total number of interviews to 17. Interviewees were sent a near-completed version of the relevant case history write-up in order to review their personal contribution, to give them an opportunity to add more detailed information, and to confirm that the representation of the case study was an accurate one, eight replied, some with minor clarifications.

To counter concerns of relatively low interviewee numbers, data was, where possible, triangulated between sources. The quality of the case histories was further confirmed in instances that did not initially entail interviews. Here, in 2 (of a total of 5) cases which were not based on interview data input was garnered from key individuals subsequent to the construction of the narratives, again with only minor clarifications and additions made. Furthermore, cases based on publicly available contemporary sources suffer less from recall bias and/or biases of individuals' perspectives.

Finally, the case histories unsupported by interview data, i.e. pazopanib and Prolarix, do not solely contribute towards the key observed trends brought out in the findings of this thesis. Here, pazopanib is merely used as a baseline case, and Prolarix has a very

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<sup>57</sup> See Appendix 2 for the information sheet, consent form and general questions asked to each of the interviewees.



similar development pathway to banoxantrone in the issues arising throughout the product life cycle.

#### **4.4.3 Steps 4 and 5 Entering the Field and Analysing Data**

Step four of Eisenhardt's theory-building method requires feedback between data collection and analysis, where both processes are implemented in parallel. This can involve the inclusion of field notes, with observations noted and any important themes highlighted. The reflective nature of this process allows the researcher to note and recall any 'cross-case comparisons, hunches about relationships, anecdotes and informal observations' (Eisenhardt, 1989:539). Step five is closely linked, and indeed forms one of the components of this iterative process. It involves the construction of detailed case study write-ups which form a systematic tool for responding to the issue of the enormous amount of data collected from the case studies in question, as Pettigrew 1988 describes it: 'death by data asphyxiation' (1988, cited in Eisenhardt, 1989:540). In addition to providing means by which the researcher can digest case-wise data, it also allows for a familiarity with the cases to develop. This facilitates the recognition and appreciation of the case as an autonomous and holistic entity.

After detailed case study descriptions were prepared, the comparative analysis was initiated. The challenges at this stage, as Eisenhardt observes, is to counter the natural human tendencies that lead to bad practice in case study analysis namely that the researcher: 'leaps to conclusions based on limited data', is 'influenced by the vividness' of the data, 'ignore[s] basic statistical properties', and 'inadvertently drop[s] disconfirming evidence'(Eisenhardt, 1989:540). One tactic highlighted in Eisenhardt's approach, is to base comparisons on similarities and differences between cases, either by categorising cases based on these, or by implementing a pair-wise comparison process (ibid).

##### **4.4.3.1 Steps 4 and 5 Implemented**

In this study Steps 4 and 5 involved collecting data, constructing the case histories and preparing the data for analysis. This was an incremental in process as it was important for an appreciation of the case studies as holistic entities to be developed (as per Eisenhardt's guidelines (1989:540)). For both analysis approaches case histories were constructed and took on a structure dictated by the framework. This involved the categorisation of data into the four main factors (knowledge base, market demand, expectations and organisational environment), as well as a chronological appreciation for the different processes under each umbrella. This necessarily involved several versions of the case studies to be constructed, include one entirely chronological account of the case history.

#### 4.4.3.1.1 *Descriptive Analysis*

The descriptive analysis largely evolved from 'getting to know' the case histories, and being able to draw out similarities and differences between them. In the first instance, in accordance with Eisenhardt's (1989) guidelines, this involved categorising the projects in line with the type of organisation (pharmaceutical company or biotechnology/academia) in which the project originated.

This analysis also progressed in an incremental fashion whereby when trends and patterns were found, it was ensured that the data supporting these assertions were triangulated and strengthened, either through personal accounts or additional data collection approaches.

#### 4.4.3.1.2 *QCA*

Section 4.2, justified the use of QCA as a component of the multiple case study approach implemented here, while 4.3 presented a historical account and overview of the logic behind QCA, this section builds on this by presenting a step-by-step account of the process of carrying out a QCA, including a discussion of the potential pitfalls and solutions to these.

The QCA approach fits well with the Eisenhardt (1989) roadmap, as Ragin (2000) also emphasises the knowledge of cases as whole entities. In the process of a QCA the main purpose of this knowledge is that it facilitates the scoring of cases in accordance with their membership into the designated 'sets' (factors/conditions) (Ragin, 2000). This process is known as calibration.

##### 4.4.3.1.2.1 *Calibration*

Once cases and conditions have been selected the data is gathered and coded into sets with scores allocated to represent membership of a set (1 for full membership, 0 for non-membership). While measurement is an absolute presentation, calibration is implemented with an emphasis placed on the relationship between the dataset and accepted standards. One specific example of calibration is in temperature where 100°C (measurement) is taken due to its association with the boiling point of water (calibration), and 0°C, the freezing point of water (Ragin, 2008:72-73). This allocation of scores is based on concept formation, echoing the approach taken by Eisenhardt (1989).

Calibration in a csQCA is facilitated due to the necessity to consider the presence or absence of a condition. So, rather than extensive vs. limited, high vs. low, positive vs. negative, supportive vs. unsupportive, it is relevant to think of full or non-membership into the set 'extensive and accumulated knowledge base', 'high expected market

demand' etc. This facilitates the process of taking data 'on balance' where discrepancies in different sources may arise.

#### 4.4.3.1.2.2 Necessary Conditions

The first step in QCA is the determination of necessary conditions. In csQCA this can be done either intuitively, i.e. by looking at each condition and assessing how it related to each outcome in terms of empirically observed cases, or through software analysis<sup>58</sup>.

Intuitively, conditions are deemed to be necessary if they are a subset of the outcome. This can be determined by producing matrices (per condition) to determine where cases in the relationship between condition (X), and outcome (Y), membership (see Table 8). This table shows that a condition is considered to be necessary when there are empirical cases where the presence of the outcome (Y=1) and the presence of the condition (X=1) are observed, but no cases observed in the presence of the outcome (Y=1) but the absence of the condition (X=0).

		X	
		0	1
Y	1	Cases should not appear for necessity	Cases should appear for necessity
	0	Cases not directly relevant	Cases not directly relevant

**Table 8 Method for determining necessary conditions (adapted from Schneider and Wagemann, 2012:71)**

Due to the asymmetrical nature of the QCA method (i.e. the findings for the presence of the outcome cannot necessarily be applied with the absence of the outcome), the analysis for necessity should be done for the presence and absence of the outcome individually.

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<sup>58</sup> There are two main software programmes that facilitate a QCA analysis. These are Tosmana (freely available at <http://www.compass.org/software.htm#tosmana>-accessed 19.3.2015) and fsQCA (freely available at <http://www.u.arizona.edu/~cragin/fsQCA/software.shtml>-accessed 31.5.2012)

#### 4.4.3.1.2.3 Truth Table

Once necessary conditions have been identified the calibrated data is presented in a matrix of cases and conditions, called a truth table. The goal of a truth table is to identify explicit connections between causal conditions and outcomes (Ragin, 2008:125). This provides an illustrative account of the combinations (configurations) of conditions that contribute towards a particular outcome (Ragin, 2008:25). Truth table construction involves assigning each row of the table a possible combination of conditions, so a study with 4 (causal) conditions, for instance, would have 16 rows in the truth table (see Table 9).

In a truth table analysis cases are assigned a combination (configuration) of conditions, in accordance with the calibrated scores. The consistency value is then assigned depending on the outcome observed for those cases. Consistency is a measure of how well the empirical observations fit with the measure (in this instance, the sufficiency of the configuration of conditions) (Schneider and Wagemann, 2012:182). For instance, where all cases under a certain configuration show the presence of the outcome they would be scored '1' and would be included in the analysis. If there was a contradiction, i.e. there were cases found for a certain configuration that showed different outcomes the consistency score would reflect this, i.e. if 50% of cases were shown to have the presence of the outcome and 50% the absence, the consistency score for that configuration would be 0.5 (see Table 9). In this instance the inclusion of the configuration into the analysis would need to be decided based on the evidence, or it might be preferential to go back to the data to attempt to resolve the configuration. Generally, it is down to the researchers knowledge of the cases to determine whether a configuration should be included into the analysis (Schneider and Wagemann, 2012).

Condition U	Condition V	Condition W	Condition X	Cases	Consistency	Inclusion
1	1	1	1	A (1), B (1)	1	1
1	1	1	0	C (1), D (0)	0.5	?
1	1	0	0	E (0)	0	0
1	0	0	0	F (0), G (0)	0	0
0	1	1	0	-	-	-
0	0	1	1	-	-	-
1	1	0	1	-	-	<u>1</u>
1	0	1	1	H (1)	0	0
1	0	1	0	-	-	-
1	0	0	1	-	-	-

0	1	1	1	I (1), J (1), K (1), L (0)	0.75	1
0	1	0	1	-	-	-
0	1	0	0	-	-	-
0	0	1	0	M (0)	0	0
0	0	0	1	N (0)	0	0
0	0	0	0	O (0), P (0)	0	0

**Table 9 Example of hypothetical truth table**

Whether a case is included in the analysis is also determined by whether it is the presence or the absence of the outcome that is being explained. If the presence of the outcome is the purpose of the analysis, then a configuration should be included if the cases observed show the presence of the outcome. Similarly, if the purpose is to explain the absence of the outcome, then a configuration should be included if the relevant observed cases show the absence of the outcome.

The configurations to be included are then combined into the analysis to produce a solution relevant to the outcome being explained. From Table 9 the solution to explain the present of the outcome would be (the presence of a condition is represented as an upper case letter, and the absence of a condition is represented by a lower case letter; and a '+' indicates either/or)

$$UVWX + uVWX \longrightarrow Y$$

The solution, which is made up of the relevant configurations is then minimised in accordance with Boolean algebra. This minimisation essentially eliminates factors that are present and absence while appearing in combination with other factors that are consistent. In this instance this would mean that 'U' is irrelevant because VWX contribute towards the outcome irrespective of the presence or absence of U. Another example is:  $AbC + abC + abc \rightarrow Y$  which can be minimised to  $bC + ab \rightarrow Y$ . The logic here is that if you take  $AbC$  or  $abC$  you can minimise to  $bC$  because the state of  $A/a$  is irrelevant to the state of the outcome if  $bC$  is present. Similarly,  $abC$  or  $abc$  can be minimised to  $ab$  (i.e. the state of  $C/c$  is irrelevant to the sufficiency of  $ab$  to the outcome).

Potential issues exist in real data that complicate the process of a truth table analysis. The above instance of contradictory truth table rows is one, i.e. where a combination of conditions is empirically observed to be associated with two different outcomes. Strategies for solving this problem include; 1) adding a new condition, 2) changing the

scope conditions in the research design, 3) changing calibration standards, and 4) redefining outcomes or memberships in sets (Schneider and Wagemann, 2012:120-121).

In addition, another common problem with using real data in QCA is the issue of limited diversity. In this discussion it is important to make clear that limited diversity is an issue observed in social reality, rather than a function of a problem with the method (Ragin, 2000:81). Limited diversity arises due to the lack of diversity seen in social phenomena, whereby certain combinations of conditions will be empirically observed numerous times, and other configurations will not be observed at all. There are configurations that theoretically exist but are not empirically observed. These are termed logical remainders (Schneider and Wagemann, 2012:152).

If the logical remainders are entirely excluded from the analysis the output is termed a 'conservative solution' (called the 'complex' solution in the fsQCA software) where all sufficient conditions (and combinations of conditions) are included and no assumptions are made about the logical remainders (Schneider and Wagemann, 2012:162). Alternatively the computer software can automatically take into account all potential possibilities for the absence or presence of the logical remainders, producing a 'parsimonious solution' i.e. the least complex solution (Schneider and Wagemann, 2012:167). However, this is deemed to be too reliant on arbitrary distinctions and therefore not suitable in most cases.

Another possible strategy to deal with the presence of a large number of logical remainders, is to attempt to envisage the counterfactual, i.e. to use the empirically observed cases and theoretical knowledge to inform the designation of a configuration as present or absent (De Meur et al., 2009:152, Yamasaki and Rihoux, 2009:143). This involves 'simplifying assumptions' which are made up of generally accepted directions of causation (directional expectations), between one or more conditions and the outcome. Simplifying assumptions can then be used to inform the treatment of the combinations that do not show empirical observations (the logical remainders) (Schneider and Wagemann, 2012:167-171). With the aid of computer software, the researcher can inform the output in this way and construct a so-called 'intermediate solution' (ibid). For instance in Table 9 we might conclude that based on theoretical knowledge it is likely that, should the combination of conditions showing the presence of U, V, X, and absence of W, have been observed in reality, it would have been associated with the presence of the outcome therefore warranting the inclusion of this configuration into the analysis (see 1 in Table 9). This is the approach that will be utilised in the analysis presented here.

The final stage of the truth table analysis is to determine the parameters of fit of the solution produced. Parameters of fit are: consistency and coverage. Consistency, as touched on above, is the extent to which the solution (or configuration of conditions) is representative in the data. And coverage is the amount of empirical data represented by a solution (or configuration of conditions) (Ragin, 2008:54).

#### **4.4.4 Step 6 – Shaping Hypotheses**

Step six from Eisenhardt's (1989) roadmap highlights the ability to bring out 'tentative themes, concepts, and possibly even relationships between variables' and apply them across different cases (1989:541). This involves a return to the constructs and may involve 'refining the definition of the construct and building evidence which measures the construct in each case' through the use of 'multiple sources of evidence to build construct measures, which define the construct and distinguish it from other constructs' (Eisenhardt, 1989:541-542).

The development of the constructs also involves a process of validation, whereby the appearance of multiple cases exemplifying a particular construct provides a logic of replication (Eisenhardt, 1989: 542). In this, in agreement with Yin (1984) cases are taken to be analogous to experiments with multiple cases (experiments) contributing towards validity through replication.

##### **4.4.4.1 Step 6 Implemented – Descriptive Analysis**

Despite the absence of this step in a QCA analysis, the descriptive analysis did involve some shaping of the hypotheses and further development of the framework in terms of the specific issues facing projects during development. These issues were compared across the case studies for the descriptive analysis.

It was these issues, highlighted from the framework development, and the associated solutions that lend themselves to differentiating successes from failures that provided the foundation for the analysis of the case histories.

#### **4.4.5 Steps 7 and 8 – Enfolding Literature and Reaching Closure**

Step seven involves the generation of hypotheses from the cross-case analysis. It is assumed, at this stage, that there will be themes and concepts emerging from the two previous steps. These are then taken and assessed in terms of how well they fit amongst the other cases. This process may involve construct definition where a single construct may begin to be defined in terms of multiple indicators. It is here that the iterative and tentative process of prior construct definition in step one bears fruit in this type of

research. In addition to the definition of constructs, verification of the relationships between constructs also contributes towards the generation of hypotheses.

The final two steps in Eisenhardt's description involve an investigation into the relationship between the hypothesis/theory generated and the existing literature, and the realisation of the point at which saturation, and therefore closure has been reached. The former is important because the acknowledgement of contradicting literature is a key point for gaining confidence in the research findings and presents an opportunity for discussion of the emergent theory in context. In the same manner, literature discussing similar findings is important because it enhances the generalisability of the research conclusions. The last step, 'reaching closure', involves the recognition of the point at which the gains from incremental learning are minimal, the saturation point.

#### **4.5 Eisenhardt and QCA**

As demonstrated in this section, and supported by the observation that QCA is a theory-building approach a QCA is well-suited to insertion into Eisenhardt's theory building approach. This is further supported by the observation that QCA is a method that fundamentally facilitates theory building (Greckhamer et al., 2013). Furthermore, QCA allows us to overcome two central issues with the method highlighted by Eisenhardt. These are i) the number of cases that can be analysed with the theory-building method (Eisenhardt 1989) and ii) the apparent weakness in the issues surrounding the complex nature of the emergent themes and findings. Here, the QCA acts to support theory building due to the ability to assess more than 10 cases (where Eisenhardt advises against investigating more than 10) and thereby produce more overarching theoretical contributions. Furthermore, the output of a QCA is in the form of distinct patterns found in the data.

The convergence of the two approaches also highlights the applicability of the methods when combined together. As will become clear, it is these three observations that make QCA a complementary addition to the theory-building case study approach.

#### **4.6 Potential Limitations of QCA and Multiple Case Studies**

Despite the apparent strength of the justification of using a multiple case study/QCA approach in the context of Eisenhardt's roadmap, rather than more qualitative or quantitative research methods, it is also appropriate to provide a discussion of the potential limitations of the method.

The iterative nature of collecting and analysing data for multiple case studies can lead to a lengthy process of adjustments and feedback loops between the data output and



theory (Berg-Schlosser et al., 2009:12, Yin, 2009, Eisenhardt, 1989). Although this iterative approach is seen as a benefit, it may cause problems in the length of time taken for such an analysis. In this context there may also be temptation for opportunistic manipulation, however, this may be resolved with an emphasis on triangulation and the use of multiple sources (Yin, 2009). Triangulation has been particularly challenging in the context of this study due to issues associated with access to data and interviewees, as discussed above, however, attention has been invested into this issue in the case histories presented below. In particular, the multiple proxies implemented provided an avenue to triangulation on a condition level.

This investment of time into increasing the quality of the empirical data collected about cases is also central to responding to a third critique of QCA and multiple case studies. This critique highlights the difficulty, of QCA and other case study-based methods, in generalising from data collected in a QCA and the wider population. In this context it is important to appreciate that despite resolving some issues associated with case study research, by assessing a larger number of cases than would traditionally be the case, there are limits to the generalisations that can be drawn from the study which will be considered in Chapter 9, as part of the discussion. However, QCA provides opportunity for deep understanding of a particular social phenomenon. Furthermore, by bringing together existing theoretical and empirical literature the framework used provides a firm foundation for further generalisation.

#### **4.7 Conclusion**

This Chapter has built on those that have gone before by explaining how the method will be used to answer the research questions presented in Chapter 1. We have presented a multiple-methods approach whereby medium N cases will be analysed and compared, within the theory-building roadmap suggested by Eisenhardt (1989). This approach is justified in four ways: 1) the ambition to draw generalisations across a number of case studies, while maintaining an in-depth analysis in order to fully understand the mechanisms at work, 2) the need to fill the gap in assessing case histories from a multidimensional framework, as identified in Chapter 3, 3) the limitations of Eisenhardt's approach, whereby the limitation in the number of case studies is overcome in a QCA, and 4) the ability to draw clear-cut and overarching conclusions from the analysis. We provided further justification for the implementation of this method in describing the lack of suitability of small N and large N approaches.

Through discussion of the step-by-step procedure suggested by Eisenhardt, while integrating QCA methods, we have presented the process by which projects will be analysed in line with the framework formulated in Chapter 3.

The methodology discussed in this Chapter will be implemented in Chapters 5, 6, and 7. Chapter 5 is a slight diversion from the aim of this thesis in providing a pilot for the case studies to come. Here it is possible to test the data collection tools, framework and operationalisation due to the triangulation made possible due to the availability of existing in-depth narratives of drug development.

Chapters 6 and 7 present the data for this thesis in presenting the case history narratives constructed using the process demonstrated in this Chapter. Throughout these discussions an ongoing descriptive analysis will also be presented comparing the similarities and differences between cases. In addition, these case histories provide the data contributing towards the calibrated QCA scores (indicating whether the case has full or non-membership into the conditions) which will be summarised and used in the analysis presented in Chapter 8.

The findings and analyses from Chapters 6, 7 and 8 will be brought together in the discussion presented in Chapter 9 which will draw conclusions and contributions for this thesis.

## 5 Path-breaking Drugs

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This Chapter provides a pilot for the empirical cases to come in Chapter 6 and 7. The purpose of this is to discuss two well-chronicled examples of drug development, Herceptin and Gleevec, where new technological approaches were utilised to create novel cancer treatments (Fischer et al., 2003). Due to the drugs presenting cases by which they are one of the first to exemplify a particular approach e.g. monoclonal antibodies and tyrosine kinase inhibitors, we term these ‘path-breaking’. For this reason, we will momentarily stray from the focus on drugs developed in the UK, whereby these projects were developed by Genentech and Novartis (Ciba-Geigy), respectively.

This Chapter has four key purposes. Firstly, these case histories demonstrate the types of issues that can occur during the drug development process and highlight solutions adopted to overcome these. Secondly, drawing on literature reviewed in Chapter 2 and 3, this Chapter illustrates some of the concepts and discussions from the literature and provide empirical evidence for these. For instance, in both Herceptin and Gleevec we witness the action of key individuals, consistently supporting the project and implementing their networks to promote development, occasionally in the face of adversity.

Thirdly, investigations into Herceptin and Gleevec also demonstrates examples of how the operationalisation of the calibration for the QCA will be undertaken, as indicated in the subtitles for each section. Finally, the discussions presented in this Chapter draw heavily on well-researched and detailed narratives documenting the drug development. Often these provide the linking assumptions on which causal inferences can be based facilitating conclusions drawn from the case histories in Chapters 6 and 7. An effort has also been made, where possible, to triangulate the observations garnered from these narratives.

### 5.1 Herceptin

The history of Herceptin has been documented in various papers and in particular a book: *HER-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer* (Bazell, 1998), which documents the history of the drug development process.

#### 5.1.1 Introduction

Herceptin (Anti-HER-2 Mab, R-597, RG-597, rhuMab HER2, trastuzumab, Ro-45-2317) is a mab, developed by Genentech and researchers at the University of California, Los Angeles (UCLA), for the treatment of breast cancer tumours. Herceptin is an example of

a novel approach to cancer therapy, utilising a monoclonal antibody to inhibit the action of a tyrosine kinase (HER2) involved in intracellular signalling and implying proliferative characteristics in HER2-positive tumour cells.

**Table 10 Herceptin development timeline**

1987	HER2/ <i>neu</i> and breast cancer association discovered and published in <i>Science</i>
1990	Roche acquire 60% stake in Genentech
1992	Phase I of Herceptin (single agent) initiated
1995	Initiation of Phase III trials
1998	FDA grant Fast Track approval for Herceptin

### 5.1.2 Knowledge Base (QCA score = 0)

The Herceptin knowledge base began with the discovery of several oncogenes and proto-oncogenes in the 1970s and 1980s. Firstly, an avian erythroblastosis tumour virus was discovered to encode an oncogene, later found to be similar to the human epidermal growth factor receptor (HER-1/ ErbB1) (Harries and Smith, 2002). Subsequently *neu* and *erbB*, later named Her-2 and *c-erbB2* were also found to be associated with overamplification in cell lines of mammary carcinomas (Harries and Smith, 2002).

At this time the research was picked up by Dennis Slamon at the UCLA, who, working with Axel Ullrich from Genentech, formalised the relationship between breast cancer incidence and HER2 (Slamon et al., 1987, Slamon et al., 1989). The next step was to produce an antibody to target HER2+ cells without affecting normal cells (Bazell, 1998). This specificity was tested in a number of antibodies produced using nude mice implanted with breast cancer cells (xenografts) (Bazell, 1998, Harries and Smith, 2002). The resulting mab was then humanised, producing Herceptin (Harries and Smith, 2002). At this stage combination treatment (i.e. the mab in conjunction with another standard cytotoxin, such as paclitaxel, cisplatin and doxorubicin) was found to show increased effectiveness (Baselga et al., 1998, Harries and Smith, 2002).

Preclinical trials provided justification for testing Herceptin in humans and phase I trials were initiated in 1992 in 16 patients with HER2+ metastatic breast cancer (Harries and Smith, 2002). An additional phase I trial testing Herceptin in combination with cisplatin was also undertaken (Harries and Smith, 2002). Phase II trials for Herceptin, in combination with cytotoxins, indicated overall response rates of around 15%, with a median response duration of 9.1 months, median survival of 13 months, median time to progression of 3.1 months and median time to treatment failure of 11 months (Harries and Smith, 2002).

Two phase III trials provided sufficient data for the approval of Herceptin. Herceptin was evaluated in 469 patients, in combination with paclitaxel and doxorubicin, and in 222 patient trials as a monotherapy (Pharma Marketletter, 1997c). Response rates from these phase III trials were significantly higher with Herceptin in combination with chemotherapeutic agent when compared to the cytotoxin as a monotherapy (45% vs. 29%; 50% vs. 38% and 38% vs. 15%) (Frankel, 2000). Overall Herceptin shows a response rate of 35% as a single agent, and this is higher when used in combination with cytotoxins (Cameron, 2007).

Fundamentally Herceptin was a novel approach and therefore suffered from a high degree of uncertainty. In addition, the target had not been previously validated successfully in a product. This supports the score of '0' for the QCA.

### **5.1.3 Market Demand (QCA score = 1)**

From discovery stages the market for Herceptin was known to be limited to the subgroup of breast and ovarian cancer patients shown to be HER2+. As will be discussed in the next section the knowledge leading up to the development of Herceptin was motivated by an association found between HER2 and breast cancer patients (25-30% of breast cancers were found to be HER2+) (Bazell, 1998, Slamon et al., 1987, Slamon et al., 1989). In addition, an association was also found between HER2 and some ovarian cancer patients (Berchuck et al., 1990, Business Wire, 1992).

This implies that Herceptin was limited to a small range of indications (breast and ovarian cancers). Furthermore, despite the common occurrence of breast cancer the market for Herceptin was small due the small subset of patients shown to be HER2+. This is quantified as around 58, 500 new cases in the USA annually. Furthermore, where the prevalence of breast cancer is around 3,000,000 (USA)<sup>59</sup> HER2+ patients would number in the region of 750,000. Despite this prevalence being larger than the 200,000 (or less) categorising 'orphan' diseases, the market estimated was small, just \$100m in sales per year sales (Pharma Marketletter, 1997d).

Breast cancer is commonly treated with a combination of surgery and cytotoxic agents such as paclitaxel and cisplatin. However, the HER2+ breast cancer subtype was found to show a particularly severe and aggressive form of the disease (Harries and Smith, 2002), implying a particular need for additional treatment for this subtype of tumours.

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<sup>59</sup> <http://seer.cancer.gov/statfacts/html/breast.html>

In this case history, despite the relatively small indication presented by the HER2+ subtype of breast cancer, comparative to rare cancers this indication provides a high market demand and has therefore been scored '1' for the QCA, representing its full membership into the set high market demand. This is further supported whereby there is a clear unmet need in this area, thereby further stimulating a positive market potential.

#### **5.1.4 Stakeholder Perspectives (QCA score =1)**

As mentioned in a section 3.1.3.3 patients made a significant impact on the development of Herceptin through the lobbying of Genentech for access to the drug during trials (Bazell, 1998, Puzanghera, 1997). In response a compassionate use programme was introduced to enable patient access to the drug, on a lottery basis, prior to FDA approval (Bazell, 1998, Puzanghera, 1997). While this was beneficial for patients Genentech were cautious, implementing a lottery system and keeping publicity to a minimum (ibid). Their concern stemmed from manufacturing issues and difficulties producing enough drug to meet demand (Bazell, 1998, Business Wire, 1997a).

In an unusual turn of events, Revlon, a large cosmetics company, became involved in the project through direct funding to Slamon (UCLA) (Bazell, 1998, PR Newswire, 1997). Despite this corporate endorsement and the associated exposure for the drug, this relationship was not publicised until late in the drug's development (Pharma Marketletter, 1997c). However, the involvement of Revlon did contribute towards breaking down the social stigma associated with breast cancer in the late 1980s and early 1990s (Bazell, 1998:71). Furthermore, Revlon benefited from the positive public image associated with aiding the development of a breast cancer drug whereby the Revlon Chairman is quoted as stating in the press: "Revlon doesn't just care about women's looks, we care about women's lives" (PR Newswire, 1997).

The role of publicity in facilitating the recruitment of patients for trials (as observed in Bazell, 1997) is exemplified in the mentions of the drug in the media. A Nexis search identifies 40 articles before beginning of 1997, 10 of these, all in 1996, in major newspapers, 21 articles in 1997 and over 300 in 1998. In particular, publicity and patient groups were key in contributing towards the recruitment of the patients required for the expanded phase III trials (Bazell, 1998:161, United Press International, 1996). The positive perspectives of the project were also constructed by Slamon promoting it in the press through discussions of trial results: "we are extremely optimistic about these trials"... "early findings are very promising, with some outstanding results" (United Press International, 1996, Papp, 1996). In addition the development of Herceptin benefited from being presented as a positive product finally arising from the hype of biotech: 'after

2 decades of hype and disappointment, a high-tech medical innovation called the mab is at last showing promise against cancer' (PM Cycle, 1996).

In summary, the hype surrounding Herceptin and the influence that the lobbying of patient groups had on the drug's development represents positive stakeholder perspectives. In addition, this positive influenced the development of the drug by promoting it. This justifies the QCA score of '1'.

#### **5.1.5 Organisational Environment (QCA score = 1)**

Herceptin development progressed as a collaborative relationship between Slamon at UCLA and Genentech (Bazell, 1998). Initially Genentech were sceptical of the project. This was for a number of reasons: 1) previous disappointment with interferon, an oncology drug which was initially thought to be applicable to a broader range of indications (Rogers, 1985), 2) the difficulty of dealing with mabs, where the first product to enter clinical trials was murine the murine mab, with a humanised version coming later (Pharma Marketletter, 1992),, and 3) the difficulty of producing an antibody for a specific single target (Bazell, 1998:47-49).

In response to these uncertainties Slamon was key in championing the project to Genentech. In this strategy Slamon was a 'tenacious lobbyist', not afraid of confrontation, and believed that if Genentech themselves did not want to develop the project they should license it out (Bazell, 1998:48). This lobbying was particularly necessary in 1989 when the Genentech senior management came close to terminating the project. In addition, lower management also came 'to the rescue' in their own championing for Herceptin (Bazell, 1998:50). As Bazell observes, in this process it is often necessary to have someone influential and internal to the company (Bazell, 1998:52).

Due to the difficulties Genentech had with the previous interferon project, oncology was not a strategic area for the company (Bazell, 1998:44) and Herceptin was their first major oncology project (Business Wire, 1997c). However, the lack of experience in oncology was partially countered by the positive impact of the firms' 'pioneer mentality' (Bazell, 1998:45) and support through being 'the first major company which is at the forefront of recombinant DNA techniques for healthcare applications' (Klott, 1980).

The Revlon funding facilitated parallel research streams for Herceptin (PR Newswire, 1997). Genentech worked on the humanisation of the mab and Slamon (at UCLA, funded by Revlon) undertook preliminary studies ascertaining the safety of the murine mabs in patients (Bazell, 1998:71).

In 1990, while Herceptin was in preclinical testing, Roche acquired a 60% stake in Genentech (Bazell, 1998:53). This reportedly stimulated a cultural change at the organisation with the arrival of a new CEO, Kit Raab, who was not enthusiastic about antibody drugs (Bazell, 1998:55-56). This may have stemmed from Raab's business-like management style where he had a reputation as an aggressive marketing executive (Fisher, 1995) and therefore presumably risk-averse approach<sup>60</sup>, where Herceptin and mabs were a risk due to the lack of previous drugs using this approach. However, the access to finance and Roche's experience did aid Genentech's ability to successfully carry out later stage trials (Bazell, 1998:133).

In these later stage trials, protocol was adapted several times due to physicians hesitation in recruiting patients who may be assigned to the 'placebo' arm (i.e. treatment with chemotherapy alone, rather than in combination with Herceptin) (Bazell, 1998:147). Suggestions that the phase III trials were run differently to those trials previously designed also implies difficulty in building on the knowledge from those that went before.

There was another change in CEO during the planning of the phase III trial, whereby Raab CEO at the time, was ousted in 1995 (Fisher, 1995, Bazell, 1998). This move was associated with several reasons. Firstly, there had been several instances of negative publicity for the company stemming from unethical sales practices resulting in ongoing legal action (Sandoval, 1995). Secondly, upon the acquisition, by Roche, of the remainder of the share capital of Genentech, the intention was to take the company in a new direction as an R&D arm of Roche, thereby implying a need for a research-focused CEO, away from Raab's management style (Fisher, 1995). Finally, and perhaps most significantly, Raab had, controversially, been found to have attempted to gain a guarantee from Roche for a \$2m personal bank loan, as part of the acquisition negotiations. This move was publicised as the former CEO taking advantage of his position and attempting to make personal gains from the situation (Sandoval, 1995). Raab was replaced with Levinson who 'promised to restore integrity to the company's business practices' (Bazell, 1998:152-153), as well as providing scientific leadership for the new direction of the company (Fisher, 1995). As well as providing a more science-driven approach for the firm Levinson also had a particular vested interest in Herceptin

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<sup>60</sup> Here, Herceptin was a risky approach due to the lack of previous products utilising monoclonal antibody techniques.



as he had co-authored a paper with Ullrich describing the cloning of the HER2 gene (Bazell, 1998:153).

Despite the sometimes questionable firm perspective of the development of Herceptin, ultimately the positive impact of Slamon as a key individual, and the access to funding and support from the Roche acquisition, enabled Genentech to take the development of Herceptin forward. This accounts for the categorisation of Herceptin as fully in the set of supportive organisational environment for the QCA (i.e. score of '1').

#### **5.1.6 Summary of Development of Herceptin**

The case history of Herceptin presented here indicates that there were doubts over the market potential of the drug, although these were overcome whereby the potential for the market stemmed from a lack of competitors in the marketplace. There were also questions over the feasibility in such a novel technological area that had not been previously validated (i.e. mabs), creating issues of risk and uncertainty. These questions, which almost led to the termination of the project, were overcome through both key individuals, who promoted the drug's development, and patients/patient groups in the advocacy and lobbying work they undertook. Furthermore, while there was a lack of strategic fit for the drug project in the Genentech portfolio, it represented a therapeutic area in which Roche is a significant player, thereby providing an avenue of growth for the parent company. Furthermore, the financial resources accessed through Roche support facilitated the development of the project.

### **5.2 Gleevec**

The history of Gleevec has been documented both in papers and the book, '*Magic Cancer Bullet*' co-authored by former Novartis CEO, Daniel Vasella (Vasella and Slater, 2003). These provide key sources for this case history.

#### **5.2.1 Introduction**

Gleevec (imatinib mesylate, STI571) is a small molecule tyrosine kinase inhibitor with specificity for Bcr-Abl, platelet-derived growth factor receptor (PDGF-R) and c-kit (Druker, 2002). Gleevec was initially developed by Novartis (formerly Ciba-Geigy) for chronic myeloid leukaemia (CML), with additional approval in gastro-intestinal stromal tumours (GIST).

**Table 11 Gleevec development timeline**

<b>1983</b>	Cancer research unit re-established at Ciba-Geigy
<b>1988</b>	First mention of tyrosine kinase inhibitors in peer reviewed publication
<b>1993</b>	Gleevec first synthesised
<b>1994</b>	<i>In vitro</i> testing of Gleevec
<b>1995</b>	<i>In vivo</i> testing of Gleevec
<b>1996</b>	Ciba-Geigy and Sandoz merge to form Novartis; Vasella bought in as CEO; first paper mentioning Gleevec published by Druker
<b>1998</b>	Phase I trials initiated
<b>1999</b>	Phase I results reported at American Society of Hematology meeting
<b>2000</b>	Compassionate use programme created through Expanded Access Programme (FDA); Phase III trials initiated; FDA fast track designation approved
<b>2001</b>	NDA filed; FDA approval

### 5.2.2 Knowledge Base (QCA score = 0)

Research on tyrosine kinase inhibitors requires the combination of several streams of research, ascertaining 1) the link between a particular kinase and cancer, 2) which subtypes are impacted by the specific tyrosine kinase, and 3) the identification of a drug to selectively target the tyrosine kinase.

In the case of Gleevec this began in the 1960s and 1970s when it was discovered that the Philadelphia chromosome<sup>61</sup> was associated with CML patients (Nowell and Hungerford, 1960, Nowell and Hungerford, 1961, Rowley, 1973), through the action of the Bcr-Abl oncogene (Vasella and Slater, 2003, Deininger et al., 2005). This discovery motivated research into investigating compounds that would be active in inhibiting the Bcr-Abl oncogene/tyrosine kinase (ibid).

The discovery of a molecule to selectively inhibit Bcr-Abl, without affecting normal cells, was challenging and met with scepticism as, at this time, no other drug had been found to successfully target a tyrosine kinase (Vasella and Slater, 2003). It was not until 1988 when Professor Alexander Levitski showed the selective inhibition of an epidermal growth factor receptor, that researchers at Novartis (then Ciba-Geigy) moved into the exploration of CML and Bcr-Abl (Vasella and Slater, 2003).

It took four years from this discovery for a compound to be produced showing *in vivo* activity. Furthermore, this compound had solubility issues that needed resolving and it wasn't until 1993 that compounds with 'drug candidate status' and promising preclinical results were identified (Vasella and Slater, 2003), with results of initial investigations

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<sup>61</sup> The Philadelphia chromosome is the product of a translocation, or swapping of material, between chromosomes 9 and 22, forming the Bcr-Abl oncogene.

published in 1996 (Buchdunger et al., 1996, Druker et al., 1996). Gleevec was chosen as it emerged as the ‘most promising ... since it had the highest selectivity for growth inhibition of Bcr-Abl-expressing cells’ (Deininger et al., 2005).

In 1994 *in vitro* studies showed that the compound inhibited 90% of leukaemia cells supporting the decision to proceed with animal studies. In 1996 Druker published the first article mentioning Gleevec in which these preclinical results were reported (Druker et al., 1996, Vasella and Slater, 2003). However, the initiation of trials in human subject was delayed due to issues associated with blood clots at the catheter administration sites. Other ‘speed bumps’<sup>62</sup> encountered with the compound included the bitter taste, impacting the potential for oral administration, and corrosive nature, damaging the machines involved in manufacturing. These needed to be resolved before phase I trials could be initiated in 1998, despite being first discussed four years earlier (Vasella and Slater, 2003).

These phase I trials showed ‘striking’ results both in safety and efficacy (Vasella and Slater, 2003:99). In particular, one patient showed complete cytogenetic response (i.e. in bone marrow not just blood) within 5 months which was previously unheard of in CML treatment (Vasella and Slater, 2003:101). In addition, at a dose of 300 mg or greater 53 out of 54 patients showed complete haematological responses, typically within 3 weeks of therapy (Druker, 2002). Furthermore, 31% of patients had a cytogenetic responses, with 13% achieving complete response (Deininger et al., 2005).

In a phase II, initiated in 1999 (Deininger et al., 2005) testing Gleevec as a single agent, data for over 100 patients was accrued, the results for which are presented in Table 12.

**Table 12 Results from Phase II trials for Gleevec (Druker 2002)**

	Chronic Phase	Accelerated Phase	Myeloid Blast Phase
Haematological response	95%	53%	29%
Cytogenetic Response	60%	26%	15%
Relapse rate at 18 months from Cytogenetic response	9%	40%	78%

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<sup>62</sup> The speed bumps described by Vasella and Slater relate to the concept of ‘project drag’ as introduced in Chapter 3. Here the former CEO of Novartis observes the frequency by which projects suffer from events contributing towards the loss of momentum for development. The appearance of a similar concept suggested by an industry expert, validates and further justifies the significance of the concept and its significance for this thesis.

Both phase I and phase II trials were designed with FDA and EMA approval in mind (Vasella and Slater, 2003). Therefore, despite the delay in phase III initiation, in the same year (2000) Gleevec fast track approval was granted to Novartis and an NDA was filed in February 2001 (Vasella and Slater, 2003, Deininger et al., 2005).

Due to the novelty of the approach used, and the lack of tyrosine kinase inhibitors prior to Gleevec we conclude that the knowledge base providing the foundation or the development of the drug is not extensive and therefore the QCA score is concluded to be '0'.

### **5.2.3 Market Demand (QCA score = 0)**

The realisation that Gleevec would only be aimed at a small market potential came early on in the drug's development and continued to be an area of contention at Novartis until late stage trials (Vasella and Slater, 2003). When the drug showed promising results in preclinical testing 'marketing managers were discouraging management from supporting the compound' (Vasella and Slater, 2003:55). In fact, when efforts at Ciba-Geigy (later Novartis) began to be aimed at cancer research and tyrosine kinases, CML and the associated Bcr-Abl tyrosine kinase target were not considered a priority due to the associated small patient population (ibid). Despite the additional potential shown in GISTs, this indication is also 'rare' and therefore did not increase the drug's market potential.

CML, which is characterised by the Bcr-Abl mutation (Deininger et al., 2005) (see *Knowledge Base* section for further discussion), typically affects 1 to 2 people in every 100,000 annually (Druker, 2002), equating to around 6,650 people in 2003 (USA) and around 1,000 people in UK (for comparison, 200,000 patients have prostate and 195,000 breast cancer) (Vasella and Slater, 2003), (Ahuja, 2000).

Despite this small potential market biotech analysts Lehman Brothers, in 2000, stated a belief that the drug could achieve blockbuster (Pharma Marketletter, 2000a). This reflects drug pricing expectations for Gleevec due to the lack of standard therapy in CML that was adequately safe and efficacious. Prior CML patient survival with standard chemotherapy was 4 years, on average, and 6 years with interferon (Vasella and Slater, 2003).

After just the phase I trials of Gleevec, substantial commercial promise was evident as Vasella observes:

'never before had any drug proven that effective [phase I results] on CML patients. Not radiation, not chemotherapy, not interferon, not Ara-C, not even the only known cure for the disease, a bone marrow transplant, which results in the death of many patients' (Vasella and Slater, 2003:13)

In summary, this section demonstrates that the market demand surrounding the development of Gleevec presented a particularly low potential, due to the small number of patients affected by the primary indication. As the blockbuster potential suggested by industry analysts was constructed from an uncertain assumption of the potential pricing for the product once launched, we score Gleevec as having the absence of high market demand, due to the limited number of additional indications it was applicable to. This justified the score of '0' for the QCA.

#### **5.2.4 Stakeholder Perspectives (QCA score = 1)**

Stakeholder perspectives were key in facilitating Gleevec's development, however, they also led to apprehension. Indeed one of the motivations for continuing the drug's development was the potential to fulfil an unmet need for patients (Vasella and Slater, 2003). However, early on, this was recognised to be a 'time bomb' due to the 'internet generation of patients' shifting from allies to enemies and having the power to cause problems for drug developers, as was the case with AIDS activists (Vasella and Slater, 2003).

Publicity for the development of Gleevec began in 1996 when Druker first published preclinical results (Druker et al., 1996). This involved a feature story in *The Oregonian* and Associated Press which served the purpose of attracting patients to trials when these were initiated in 1998 (Vasella and Slater, 2003). This is key to overcoming the common problem with many orphan drug projects, where patient recruitment to trials, due to the sheer lack of patients afflicted, can be challenging.

Patient demand also promoted the acceleration of Gleevec manufacturing and development efforts, particularly when patients clamoured for access upon positive trial results (Vasella and Slater, 2003). Indeed some trial results were purposefully kept secret in order to contain patient response and avoid raising false expectations (Vasella and Slater, 2003). This fear, of a 'patient revolt' was realised in 1999 when a patient-led petition received over 3,000 signatures in under a month leading to a request to Novartis for 'assurance that everything will be done to produce a sufficient supply of STI571 [Gleevec] to ensure that the trial investigators [were] not held up in any way at all in trialling this new drug and in advancing to the certification that we anticipate' (Vasella and Slater, 2003:110-117).

In 1999 TV and newspaper coverage of the presentation of trial results at the American Society of Hematology meeting instigated 2000 calls a day to Novartis (Vasella and Slater, 2003). For instance, on 28<sup>th</sup> December 1999 the drug was described as a 'wonder drug' bringing 'real hopes of a cure' (Houldcroft, 1999). Vasella and Slater reflect that this demand arose from a generation of 'internet activists' and empowered patients (Vasella and Slater, 2003). In response to patient pressure, and despite the company's reservations, Novartis did create a compassionate use programme in June 2000, under the Expanded Access Program at the FDA (Vasella and Slater, 2003).

Media reports confirm the enthusiasm for the drug where it is described as a 'wonder drug' in 1999. In addition patient stories report positive reactions to treatment with the drug (Ahuja, 2000, Koglin, 2000, Kalb, 2000, Allison, 2000, Cardy, 2000). However, there are also reports of physicians being uncomfortable with not being able to prescribe the drug more widely, prior to the introduction of the compassionate use programme (Ahuja, 2000). In addition the 'patient revolt' is also publicised in 2000 where supplies were described as limited and 'patients around the world [were] clamouring for a new pill [Gleevec]' (Allison, 2000).

The oral administration of the drug also justified support from physician and patient stakeholders. Vasella observes: 'capsule allows most patients to lead a normal life' (Vasella and Slater, 2003:25).

Stakeholder perspectives surrounding Gleevec development were positive, with enthusiasm felt for the drug, particularly from patients. This demonstrated a positive stakeholder perspective and justifies the QCA score of '1'.

#### **5.2.5 Organisational Environment (QCA score = 1)**

The development of Gleevec was carried out in-house at Novartis (formerly Ciba-Geigy) with some early work also undertaken by researchers at the Dana Farber Institute (Vasella and Slater, 2003).

In the early 1980s Ciba-Geigy closed their cancer research unit due to the perceived lack of prospects in the field: 'management simply decided the investment was not worth the paltry returns' (Vasella and Slater, 2003). However, in 1983 Ciba-Geigy re-established an oncology unit, headed by Alex Matter, who championed Gleevec's development (Vasella and Slater, 2003). This process involved promoting the drug in the face of opposition and suggestions to terminate development. Vasella and Slater recall: 'he [Matter] knew that people were tired of hearing from him. But he did not care' (Vasella and Slater, 2003:62). Matter also utilised his networks to bring in other key individuals

for the project: Nick Lydon and Brian Druker (Dana-Farber Institute) (Vasella and Slater, 2003).

Druker's involvement, in testing candidate products, was short lived as Ciba-Geigy's main competitor, Sandoz, began a collaboration with the Dana-Farber Institute. During this time the Ciba-Geigy cancer research unit increased in numbers to 100 researchers (Vasella and Slater, 2003). However, in 1996 Sandoz and Ciba-Geigy merged to produce Novartis, where upon Vasella was brought in as CEO and Druker could return to work on the Gleevec project (Vasella and Slater, 2003).

Vasella developed a personal interest in Gleevec due to the continued championing of the project to him by Matter (Vasella and Slater, 2003). However, this support was met with continued scepticism in other areas of the organisation due to the lack of credibility of the previously unproductive cancer research unit:

'even with the degree of support that I was showing the project, there were enormous pressures on Alex Matter's team, pressures that spelled trouble for the compound seemingly at every turn' (Vasella and Slater, 2003:61).

However, Vasella did have the power to continue the drug's development despite a perceived lack of commercial viability:

'I [Vasella] suggested that if a compound proved promising if it seemed likely to be medically significant, it made no sense to halt the research because of weak commercial projections' (Vasella and Slater, 2003:62).

Organisational culture has been observed to be integral to the Novartis approach and, in particular in the development of Gleevec:

'[the organisation] learned to grapple with high risk by giving our researchers as much freedom as possible without losing focus and alignment' (Vasella and Slater, 2003:94)

Indeed the shift in organisational culture at Novartis post-merger was key to researchers feeling a sufficient level of freedom to explore opportunities (Vasella and Slater, 2003).

The organisational environment surrounding the development of Gleevec stems from the consistent involvement of Novartis (in-house) and the action of key individuals to promote the drug's development within the firm. This contributes to the QCA score (1).

### **5.2.6 Summary of Development of Gleevec**

Gleevec presents an interesting development trajectory due to the low market demand characterised by CML. The technological approach was novel, underexplored and uncertain prior to the development of Gleevec and was therefore met with scepticism. This case history exemplifies the influence of a several project key individuals in championing the development of a drug, through sourcing new expertise from their networks and continuing support for drug development throughout its life cycle. In addition, Gleevec's success can also be associated with the influence of patients in the development process, and in particular in the pressure placed on Novartis to accelerate development and introduce a compassionate use programme. This is also taken in the context of the drug showing significant effectiveness in an area of unmet need.

## **5.3 Summary and Conclusion**

This chapter has provided case histories of to two 'path breaking' drug projects providing a foundation for subsequent empirical chapters (6 and 7). The projects are termed 'path breaking' as they represent the first instance in which new technological approaches (mabs and small molecule tyrosine kinase inhibitors) have been implemented in drug discovery and development.

This Chapter has demonstrated the utility of the framework constructed in Chapter 3, outlining a multi-dimensional approach, while highlighting the importance of four conditions for successful drug development. In addition, we have drawn on the literature review by illustrating the concepts and theories discussed. This is exemplified whereby we can illustrate some of the solutions suggested to be integral to overcoming issues encountered during project development. Here we have identified, in Herceptin and Gleevec, illustrations of four of the seven possible mechanisms suggest to be integral to overcoming issues and thereby convey project success.

These discussions have further provided us with the mechanisms we can draw on to form inferences in the case histories to come in the following Chapters (6 and 7), whereby detailed narratives by those involved allows us to see a clear picture of the mechanisms at work. For instance, we have witnessed the action of key individuals, in both Herceptin and Gleevec, the positive impact of corporate image on providing support for a development project, as in the involvement of Revlon in Herceptin, and the role of patient demand in guiding development, again in both case histories.

For instance, we can equate the introduction of a compassionate use programme to the perception, by the firm, of a strong patient demand, promoting the accelerated



development of the project. In addition, where positive results of trials, we see patients responding and lobbying firms, particularly where there is a clear unmet medical need. As Vasella and Slater (2003) observe the power of a new age of internet activists, representing the acknowledged power of patients and the influence of the media on drug development. In addition, we have seen how novel technological areas, while met with enthusiasm from researchers, can also be associated with scepticism and uncertainty.

We have demonstrated how data can be gathered from documentary evidence complemented by narratives (in this Chapter by books, in the following Chapters in the most part through interviews), something which will be emulated with interview accounts in the case histories to come. In addition, QCA calibration has been carried out demonstrating the operationalisation highlighted in the previous Chapter.

Furthermore, this Chapter has validated and justified the introduction of the concept of 'project drag' whereby we witness that small adverse events, if not overcome, are perceived to be detrimental to project development.

The following Chapters (6 and 7) build on these pilot cases, whereby the main empirical evidence for this thesis is presented, in the same format and using similar sources to those presented here, albeit without the presentation of pre-conducted narratives discussing drug development.

## 6 Analysis of Rare Cancer Drug Development in Big Pharma

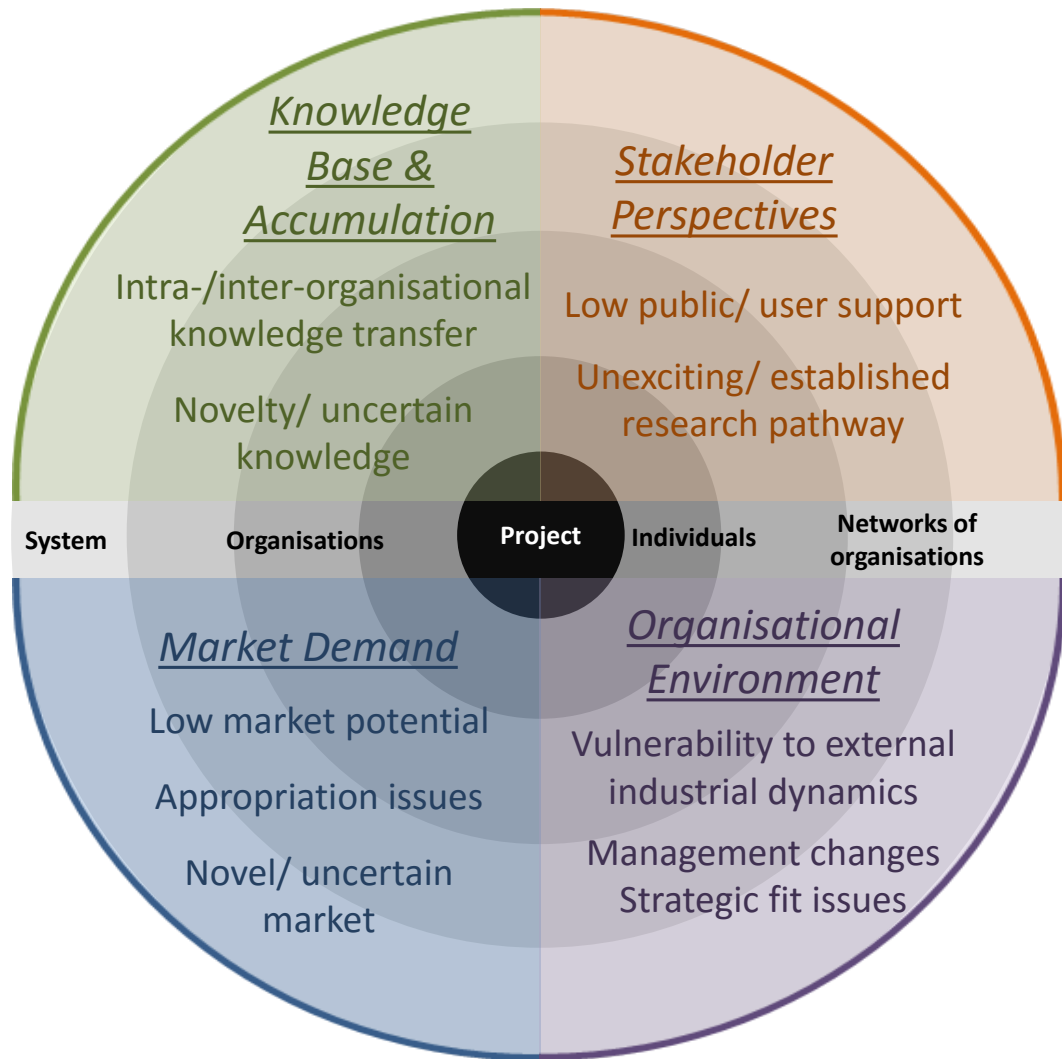
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### 6.1 Introduction

This Chapter presents the first of three analyses Chapters (6, 7 and 8) comprising, in total, 11 drug project case histories, identified using the selection criteria described in Chapter 4. Each case history will be presented, with the main findings drawn out of each reflecting back to the framework constructed in Chapter 3. As discussed in Chapter 4 this thesis uses a case-wise comparison methodology in which cases are compared to each other in terms of the four conditions highlighted in the framework (Figure 5), namely: knowledge base/accumulation, market demand, stakeholder perspectives and organisational environment. In addition, in the context of the case history the QCA score will also be assigned. The scores for the QCA will be analysed in Chapter 9.

The data and analyses presented in the following chapters have been separated between cases originating in big pharma (this chapter) and smaller biotech/academia (Chapter 7). Four of the twelve projects in this thesis were initiated in pharmaceutical firms (GSK and AZ). Two of these (pazopanib and barasertib) were developed in-house (at GSK and AZ, respectively) and two (nelarabine and plevitrexed) were the result of collaborative relationships between big pharma and academic research labs.

In investigating projects arising from research in big pharma, we observe an ideal-type case in pazopanib which followed an apparently unproblematic development pathway providing a baseline for comparison with other projects that are deemed to have suffered more difficulties. In addition, the findings indicate that in big pharma, projects tend to be terminated due to a process of 'project drag'. Here we find that market-, efficacy- and strategy-related issues accumulate and contribute towards and eventual decision to discontinue development, due to a loss of momentum. We also witness, in the case of nelarabine, a challenging development trajectory overcome by the action of a consistent and effective research team and the presence of an influential key individual.



**Figure 5 Summary of framework developed in Chapter 4**

## **6.2 The Baseline - Pazopanib**

Pazopanib hydrochloride (786034, armala, SB786034, Votrient) provides a baseline because development progressed unproblematically and was successfully developed by a big pharmaceutical firm.

### **6.2.1 Interview sources**

No interviews were undertaken to inform this case history<sup>63</sup>.

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<sup>63</sup> It is possible that the lack of qualitative evidence in the form of interview data may account for the lack of identification of issues during the project's development. However, it is expected that should issues raised during development have been significant they would have been identified from other documentary evidence.

### 6.2.2 Introduction

Pazopanib is a multi-target tyrosine kinase receptor inhibitor primarily indicated for renal cell carcinoma (RCC). It was discovered and developed at GlaxoSmithKline (GSK) (previously SmithKline Beecham) during the period from 2002 to 2009, when it was first approved in USA for advanced RCC.

<b>1988</b>	First mention of tyrosine kinase inhibitors in peer reviewed publication
<b>1989</b>	SmithKline Beckman merge with Beecham
<b>1995</b>	Glaxo merge with Burroughs Wellcome
<b>2000</b>	Glaxo Wellcome merge with SmithKline Beecham
<b>2002</b>	Pazopanib Phase I trials initiated
<b>2003</b>	Pazopanib Phase II trials initiated
<b>2005</b>	Pazopanib Phase III trials initiated
<b>2006</b>	Sunitinib (Pfizer tyrosine kinase inhibitor - competitor) approved for RCC
<b>2009</b>	Pazopanib approved for use in RCC; Sunitinib approved for 1 <sup>st</sup> line treatment of RCC by NICE
<b>2011</b>	Pazopanib recommended as 1 <sup>st</sup> line treatment for RCC

**Table 13 Key events in the development of pazopanib**

### 6.2.3 Knowledge base (QCA score = 1)

Pazopanib entered trials two years after the SmithKline Beecham (SKB)/Glaxo Wellcome (GW) merger (2000). The project originated from research at SKB, where it was known as SB786034, who were named as assignee, in a patent filed around the time of the merger (Bolor et al., 2007, Bolor et al., 2006, Bolor et al., 2012). Both GW and SKB both had prior capabilities in kinase inhibitors, evidenced in the firm portfolios, with pazopanib at SKB and the kinase inhibitor lapatinib (Tykerb/GW572016) developed by GW, shown to be in trials in 2000 (GlaxoSmithKline plc, 2000).

Tyrosine kinases<sup>64</sup> (such as pazopanib) were initially used to target the vascular epidermal growth factor 2 receptor (VEGFR2)) (GlaxoSmithKline plc, 2002). The VEGFR pathway has also been previously validated in many drugs, including the mab bevacizumab (Avastin) (first approved in 2004 for colorectal cancer), and small molecule

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<sup>64</sup> Also refer to Chapter 2, Section 2.3 for a detailed discussion of each of the cancer therapeutic subclasses referred to in these empirical Chapters.

tyrosine kinase inhibitors such as sunitinib (first approved in 2006 for gastrointestinal stromal tumours) and sorafenib (first approved in 2005 for RCC).

Pazopanib was tested for multiple kinase activity in preclinical studies (in vitro) (GlaxoSmithKline plc, 2007a). The drug was shown to be effective against the following tyrosine kinases: the VEGFRs -1, 2, and 3, platelet derived growth factor receptors (PDGFR) - $\alpha$ , - $\beta$ , B-Raf and C-kit (Kumar et al., 2007). However, the VEGF pathway was the most well characterised in human tumours, with publications throughout the 1990s describing its activity, including in lung (Volm et al., 1997b, Volm et al., 1997a), breast (Brown et al., 1995, Yoshiji et al., 1996), gastrointestinal (Brown et al., 1993b, Suzuki et al., 1996, Ellis et al., 1998, Uchida et al., 1998), kidney (Brown et al., 1993a, Nicol et al., 1997, Tomisawa et al., 1999), bladder (Brown et al., 1993a), ovarian (Olson et al., 1994, Sowter et al., 1997, Yamamoto et al., 1997), endometrium (Guidi et al., 1996), glioblastoma and other intracranial tumours (Shweiki et al., 1992, Plate et al., 1992, Phillips et al., 1993)). This may be the reason behind the delay in reporting the multi-kinase activity of pazopanib. However, it is now recognised that multiple kinase inhibitors generally have higher levels of efficacy due to the various pathways they act on (Gotink and Verheul, 2010).

A large number of publications were found mentioning the two main kinase targets, VEGFR and PDGFR in a PubMed search: 4,119 for PDGFR and 2,813 articles for VEGFR<sup>65</sup>. This represents a large knowledge base supporting investigations into the pazopanib drug target, up to and including the year the drug entered phase I clinical trials (2002).

Between 2002 and the end of 2010 (the year prior to pazopanib's FDA approval), over 100 trials are reported in the clinicaltrials.gov database for the drug. From the published results, strong responses in a variety of solid tumours, in particular in RCC (responses in 6 out of 6 patients), were reported for phase I trials (Cancer Drug News, 2005). Phase II results were similarly encouraging: 31% of 35 patients with ovarian cancer showed a response<sup>66</sup>(AFX International Focus, 2007b), 30 out of 35 lung cancer patients showed tumour shrinkage by up to 85%, and of 225 patients with RCC, 27% showed a response

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<sup>65</sup> The search terms used were as follows: ((PDGF AND receptor) OR ("platelet derived growth factor" AND receptor)) AND ("1900/01/01"[Date - Publication]: "2002/12/31"[Date - Publication])

<sup>66</sup> Where a response was defined by a greater than 50% decreasing in CA-125 protein blood levels (taken as an indicator that the tumour was not growing).

and an additional 46% of patients showed a stable disease (AFX International Focus, 2007c).

Pazopanib phase III trials initially focused on 435 RCC patients (Pharmaprojects). The results indicated an average progression free survival of 9.2 months (compared to 4.2 months in a control group), the risk of progression or death was decreased in 54% of cases and the overall response rate was 30%. Additional phase III trials were undertaken in 2009 for epithelial, fallopian and peritoneal cancers and in 2010 for non-small cell lung cancer (Pharmaprojects).

In addition to the knowledge base surrounding the target and drug, it is also relevant to consider the disease-based knowledge relevant to the development of the project. In this case RCC (the primary indication) displays a relatively small number of publications, taken to contribute towards its understanding (9,489<sup>67</sup>, up to and including 2002, the year trials were initiated).

This history of the knowledge base surrounding the development of pazopanib indicates that the project had a relatively unproblematic journey to approval, involving the steady accumulation of knowledge throughout discovery, validation and trials. Despite the novelty of the approach used in pazopanib, i.e. targeting tyrosine kinase receptors, which may have led to uncertainty, the validation of the pathway (i.e. target-disease link) and extensive trials undertaken provided an extensive and accumulated knowledge base for the drug. These factors justify the full membership of pazopanib into the set 'extensive and accumulated knowledge base' and therefore the QCA score of '1'.

#### **6.2.4 Market demand (QCA score = 1)**

As with many drug projects developed for rare cancers by large firms, pazopanib was explored in several indications (according to Pharmaprojects). According to Pharmaprojects, in addition to the RCC primary indication, the following secondary cancer indications are also listed: breast, non-small cell lung, general sarcoma, ovarian, peritoneal, fallopian tube, nasopharyngeal, soft tissue sarcoma, brain, cervical, leiomyosarcoma, pancreatic, gastrointestinal, myeloma, synovial sarcoma, neuroendocrine carcinoid, neuroendocrine pancreatic, bladder, liver, psoriasis, colorectal, thyroid, head and neck, oesophageal, endometrial and gastrointestinal

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<sup>67</sup> This figure was obtained using the Medical Subject Heading (MeSH) term 'Carcinoma, Renal Cell' as a search term in PubMed.

stromal tumours. Therefore, despite the primary indication, RCC, being classified as a 'rare cancer' the drug had a broad market potential.

Initial development in a rare indication, with other markets following post-initial approval, is a strategic approach to the development of orphan drugs by big pharma, particularly in cancer (Meekings et al., 2012). This usually reflects the desire to gain access to regulatory policies (e.g. orphan drug status), however, this did not occur in the case of pazopanib. In this instance the reason for the development of RCC as the primary indication is due to the high efficacy found in trials.

In preclinical studies, pazopanib was found to inhibit tumour growth in a broad range of human tumour xenografts in mice (Kumar et al., 2007). Broad applicability of pazopanib is further exemplified in press reports where it is described as being active in multiple cancer types (UPI, 2005). Phase I trials were undertaken showing activity in patients with RCC, gastrointestinal, neuroendocrine, lung, thyroid tumours and sarcomas (GlaxoSmithKline plc, 2005). However, in phase II investigations GSK introduced a level of specificity in the pazopanib strategy where three trials were performed, in RCC, ovarian cancer, fallopian tube or peritoneum and soft tissue sarcoma (AFX International Focus, 2007c, AFX International Focus, 2007b, GlaxoSmithKline plc, 2007b). Subsequently phase II trials were also carried out in relatively common cancers such as recurrent prostate cancer, breast cancer, glioma and lung cancer (clinicaltrials.gov). Prior to pazopanib approval phase III trials were initiated in RCC, sarcoma and ovarian (GlaxoSmithKline plc, 2008, Thomson Financial News Super Focus, 2008). This shows that the broad potential for the drug was actively being explored as part of the pazopanib development strategy.

Despite the characterisation of the pazopanib primary indication as a rare disease, early in the drug's development (2005) industry stakeholders estimated the revenue size to be large. For instance, for four of the GSK oncology-related therapeutics (pazopanib, eltrombopag, lapatinib and casopitant), revenues are estimated to be \$4bn a year (Investor Chronicle, 2005). This projection of high market potential continues for the subsequent years when in 2007 pazopanib is described as having 'huge market potential' in a variety of tumour types (AFX International Focus, 2007a).

In addition to the large projected market size for the pazopanib, and the potential for it to be applied in a broad range of cancer types, the drug lacked competitors due to RCC being an area of unmet need. Prior to 2006 the year pazopanib was in trials, there was no standard treatment for patients with advanced or metastatic RCC whose treatment

did not respond to 1<sup>st</sup> line immunotherapy (National Institute for Health and Care Excellence (NICE), 2009).

In 2006, sunitinib, another tyrosine kinase inhibitor, was approved (ibid). This approval impacted the potential predicted pricing level of pazopanib, as the value placed on drugs by NICE<sup>68</sup> technology assessments are based on standard treatments. However, the recommendation by NICE for sunitinib (as a first line therapy for advanced and metastatic RCC patients) may have had the opposite effect, in encouraging GSK through the potential to demand a premium price. This was confirmed in 2011 when pazopanib replaced sunitinib as the NICE-recommended first line treatment for patients with advanced RCC (National Institute for Health and Care Excellence (NICE), 2011).

This section has highlighted the large expected market demand of pazopanib, demonstrated through: 1) the broad applicability of pazopanib in a diverse range of cancer indications, 2) the high expected revenues identified from analysts' views projects in media reports and 3) minimal competition in the RCC market, with sunitinib only approved three years prior to pazopanib.

#### **6.2.5 Stakeholder Perspectives (QCA score = 1)**

As a kinase inhibitor, pazopanib benefitted from the exciting prospects associated with this approach to advancing cancer therapeutics. In addition to the scientific community, other stakeholders also had high expectations for the project. One of the drug's first mentions in a newspaper claimed that GSK had high hopes for pazopanib, but is as an adjunct to an article focusing on another GSK kinase inhibitor, lapatanib (Tykerb) which is described as a 'new 'wonder drug' (Hope, 2005).

Other mentions of pazopanib in newspapers (The Guardian, The Times and The Daily Telegraph) appear in December 2005 when GSK released information about their growing oncology pipeline, describing pazopanib as one of their most exciting projects (Reece, 2005, Moore, 2005, Irving, 2005). However, the Daily Telegraph article, in addition to promoting positive expectations of pazopanib, does not present GSK in a positive light. The article is headlined: 'Make the sick pay, says Garnier GSK chief says governments must compel patients to fund own healthcare', and quotes the GSK chief executive as promoting a co-payment system for expensive oncology products, including

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<sup>68</sup> NICE (National Institute of Health and Care Excellence) provides recommendations for prescriptions in the UK's National Health Service. Furthermore, their technology assessments of cost-benefit analyses of prescription drugs are also used by other countries.



pazopanib (Reece, 2005). Pazopanib appears in newspapers again in the following year where the GSK CEO is quoted as having high hopes for the drug despite having being hit by high profile failures (Ashton, 2006).

Additional positive perceptions of the drug would be expected to have resulted from an article in The Times in June 2007 describing a 'money back' pricing arrangement where GSK agree to help cover the cost of drugs, including pazopanib, if patients failed to show progress (Pagnamenta, 2007). In the same month GSK announce plans to release five new cancer drugs by 2010, including pazopanib, which leads a series of newspaper articles being published mentioning pazopanib (Cunliffe, 2007, Barriaux, 2007, Attwood, 2007, Toronto Star, 2007)

Furthermore, pazopanib is administered orally, which is less invasive than intravenous administration and preferable for patients and physicians.

The stakeholder perspectives surrounding pazopanib indicate a positive condition surrounding its development. This is not only in terms of the support for the therapeutic approach, i.e. in the use of kinase inhibitors, but also through the ease of administration contributing towards a positive perspective by users (physicians and patients). In conjunction with the projection of high expectations of the drug by GSK in the press, indicates that pazopanib is representative of full membership into the set 'positive stakeholder perspectives' therefore justifying the QCA score of '1'.

#### **6.2.6 Organisational environment (QCA score = 1)**

Pazopanib was discovered and developed from an in-house project at GSK. GSK is a large pharmaceutical company that was formed from the merger of two established companies, SKB and GW, in 2000. Both had experience and capabilities in oncology with two marketed oncology drug products mentioned in the first annual report for the enlarged company (Hycamtin for ovarian and small cell lung cancer, and Navelbine for non-small cell lung and breast cancer) (GlaxoSmithKline plc, 2000). Of these Hycamtin originated at SKB and Navelbine originated at GW (Burroughs Wellcome (BW) prior to the merger) (PR Newswire, 1994, PR Newswire, 1996). It would be expected that the merger would have been disruptive to the operating of GSK in 2000; however, this was relatively early on in the discovery stages of pazopanib. Furthermore, over the subsequent years the strategy of the enlarged company towards targeted therapeutics provides a positive environment for pazopanib.

The first indication of a strategic shift at GSK towards oncology, and later to targeted therapeutics is illustrated in press articles in 2005 which are quoted: 'GlaxoSmithKline ...

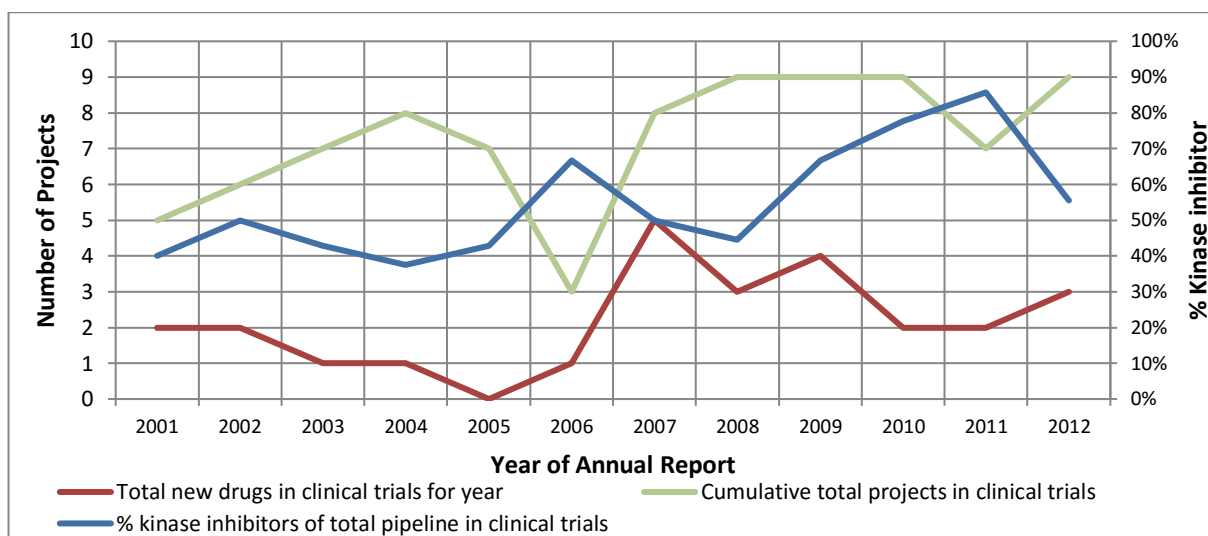
is significantly expanding its oncology drug pipeline' (UPI, 2005), 'GlaxoSmithKline Presents Rapidly Expanding Pipeline of Oncology and Supportive Care Compounds' (GlaxoSmithKline plc, 2005).

The strategic role of oncology for the GSK business is further highlighted by Tachi Yamada, GSK's Chairman of R&D, who is quoted as saying:

'Today's seminar clearly shows the progress GSK has made in building its oncology pipeline... From modest beginnings, we now have a pipeline which is one of the largest in our industry with seven major assets expected to be in phase III development in the coming months, including the four NCEs [pazopanib] highlighted today' (GlaxoSmithKline plc, 2005).

In the same article, Paolo Paoletti, Senior Vice President of GSK Oncology Medicine Development Center adds 'GSK is pursuing therapies targeting cancer at a molecular level in order to block biochemical pathways that transform normal, healthy human cells into cancer cells' (GlaxoSmithKline plc, 2005).

An analysis of the GSKs oncology pipeline also indicates some interesting trends. Firstly, a peak, in 2006, in the number of oncology drugs in trials (see Figure 6). Secondly a trend for increasing the number of kinase inhibitors in the pipeline (Figure 6). The percentage of the pipeline that are kinase inhibitors peaks as high as 86% (or a ratio of 7:2) in the 2011 annual report (Table 14). Pazopanib was one of the first kinase inhibitors in the pipeline, with only lapatanib (approved as Tykerb in 2007) and elacridar (discontinued in 2006) entering trials beforehand.



**Figure 6 Graph of changes in GSK Oncology Pipeline. Right hand axis indicates % of kinase inhibitors (% of total pipeline in clinical trials); left hand axis indicates number of projects (both total new drugs in clinical trials for year and cumulative total project in trials).**

Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Kinase inhibitor projects in trials	1	2	3	3	3	3	2	4	4	6	7	6	5
Non-kinase inhibitors in trials	2	3	3	4	5	4	1	4	5	3	2	1	4
% kinase inhibitors of development pipeline	33%	40%	50%	43%	38%	43%	67%	50%	44%	67%	78%	86%	56%
Total new drugs in trials for year	-	2	2	1	1	0	1	5	3	4	2	2	3
Cumulative total projects in trials	3	5	6	7	8	7	3	8	9	9	9	7	9

**Table 14 Raw data showing numbers of drug projects in the oncology portfolio of GSK between the years 2000-2012. Data taken from GSK annual reports**

The increase in cumulative oncology projects (Figure 6) indicates a strengthening of this area in the GSK pipeline, despite both SKB and GW previously having successful cancer drugs. Furthermore, kinase inhibitors make up a major proportion of the oncology pipeline by the late 2000s. This indicates that targeted oncology projects such as pazopanib, were key to the GSK strategy.

It is not expected that the mergers between SKB and GW would have caused disruption for pazopanib as the event occurred early on in the project. This contributes towards the seamless development progression of pazopanib, justifying the QCA score of '1' indicating full membership into the set representing a supportive organisational environment.

### 6.2.7 Pazopanib Conclusion

The development of pazopanib progressed unhindered. Here, the project benefitted from a rapid development (9 years from first synthesis to approval)<sup>69</sup> for a range of potential indications that implied a large market potential.

The project was developed using a novel technological approach that may have been subject to technological and market uncertainties. However, positive expectations (both from the scientific community, the firm and users) and previous pathway and target validation in approved products, counteracted the influence of this uncertainty.

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<sup>69</sup> For comparison clinical trials (after preclinical testing of the synthesised drug is undertaken) last around 8 years for oncology drugs (22 months for phase I, 29 for phase II and 47 for phase III) (Abrantes-Metz et al., 2004), with total duration from patent to commercialisation demonstrated to have risen to around 13.9 years in the 2000s (Pammolli et al., 2011).

Furthermore, pazopanib benefited from a supportive organisational environment, where it was part of a strategic focus on oncology and tyrosine kinase inhibitors for cancer indications. We can assume that, due to the extensive experience and the technological competencies at GSK, routinized knowledge sharing between teams existed. Furthermore, the case history suggests no complications within inter-organisational knowledge transfer requirements.

### **6.3 Barasertib – When Promise Disappoints**

Barasertib, like pazopanib, was a small molecule kinase inhibitor developed in-house at a big pharma. In contrast, however, the development of barasertib was not straightforward.

Barasertib (AZD1152) exemplifies a case where issues such as low market expectations, novelty/uncertainty of target market, uncertainty in knowledge base and lack of public support for the project contributed towards project termination. Ultimately, the project suffered from a lack of understanding of a novel technological area and disappointing market and activity expectations. Furthermore, barasertib provides a good example of how project drag, from an accumulation of issues, can contribute towards failure. For instance, low potential market demand, false predictions/uncertain knowledge foundation and the lack of media/stakeholder coverage.

#### **6.3.1 Interview sources**

One interview was undertaken for this case history, referred to as interviewee F.

#### **6.3.2 Introduction**

Barasertib was a small molecule aurora B kinase inhibitor aimed at acute myeloid leukaemia (AML). Development was undertaken by AstraZeneca (AZ) resulting from a collaboration with SUGEN (2005-2010). In 2011 the AZ annual report states that the development of barasertib was discontinued for economic reasons.

<b>1995</b>	Zeneca-SUGEN collaboration begins focusing on kinase inhibitors
<b>1998</b>	Aurora 2 overexpression discovered and published by SUGEN scientists
<b>1999</b>	Astra and Zeneca merge to form AZ
<b>2000</b>	Gemtuzumab approved for AML patients (competitor for the AML market)
<b>2001</b>	Gleevec (kinase inhibitor) approved (providing proof of concept for kinase inhibitors)
<b>2005</b>	Barasertib (AZD1152) enters Phase I
<b>2009</b>	Barasertib (AZD1152) enters Phase II
<b>2010</b>	Barasertib (AZD1152) enters Phase III
<b>2011</b>	Barasertib (AZD1152) discontinued by AZ

**Table 15 Key events in development of barasertib**

### 6.3.3 Knowledge base (QCA score = 0)

When the human form of aurora kinases were discovered by SUGEN, the *aurora 2* gene was hailed as a ‘oncogene<sup>70</sup>’ both in the scientific literature (Bischoff et al., 1998), and by SUGEN themselves: ‘*SUGEN and Zeneca discover new oncogene, Aurora2, overexpressed in more than 50% of colorectal cancers and subsets of other tumor types*’ (SUGEN, 1998). The associated logic was that if the gene could be inhibited then cell proliferation, and therefore cancer, could be stopped (Keen and Taylor, 2009).

In line with the terms of the discovery agreement (discussed further under the ‘organisational environment’ section) between AZ and SUGEN, the tyrosine kinase target passed to AZ (Zeneca at the time), for high throughput screening, lead optimisation and preclinical and clinical development (SUGEN, 1998). The high throughput screening, used to identify an aurora kinase inhibitor, identified a quinazoline derivate, ZM447439 (Coumar et al., 2009).

Despite not being suitable for administering to patients ZM447439 was a useful tool for biological characterisation, from which a clinically useful drug product could then be developed (interviewee F) to ascertain the type of aurora kinase that was being targeted (i.e. A or B; 1 or 2<sup>71</sup>). Initially it was found that ZM447439 inhibited both Aurora A and B

<sup>70</sup> An oncogene is a gene found to lead to cancer, usually through the inhibition of natural cell death causing abnormal growth.

<sup>71</sup> When the aurora kinases were initially discovered the targets were referred to as aurora 1 and 2, however as knowledge surrounding the targets developed these came to be known as aurora A (previously aurora 2) and aurora B (previously 1) kinases (Aurora Kinase (Aur) family: aurora kinase A from Guide to Pharmacology

(Coumar et al., 2009), upon which an investigation into the phenotypic responses associated with each kinase inhibitor was undertaken (Girdler et al., 2006). These studies indicated that aurora B kinase showed an anti-proliferative effect and so presented an 'attractive' anti-cancer target (Girdler et al., 2006, interviewee F). It was this stream of work that led to the filing of a series of patents by AZ, contributing to barasertib (Jung and Pasquet, 2005, Jung and Pasquet, 2003, Anderson et al., 2007, Heron et al., 2004, Coumar et al., 2009).

While this work was undertaken by AZ, Vertex Pharmaceuticals Inc., a US Biotechnology company, conducted the first preclinical testing of an aurora kinase, VX-680, (Vertex Pharmaceuticals, 2003). These tests showed tumour regression in animal models seemingly validating aurora kinases as a target for cancer drugs (Coumar et al., 2009).

As previously mentioned, initial investigations into aurora kinases described them as oncogenes. However, subsequent research indicated that they were in fact active mitotic agents, similar to classic cytotoxins such as paclitaxel and vincristine (Keen and Taylor, 2009, interviewee F). This changed the understanding of how aurora kinases act in their action in cell growth and tumour inhibition.

A lack of understanding about drug-target-disease interactions is a reoccurring trend in genomics era drugs (Hopkins et al., 2007). Even in the early stages of barasertib development there were doubts in the ability of the molecule to act on cancer. Keen and Taylor, researchers from AstraZeneca and University of Manchester who were involved in the development of aurora kinase inhibitors (including ZM447439 and barasertib), observe that while there is now considerable data supporting a link between Aurora A and B kinase expression and cancer, more work is required in understanding their mechanism of action and how they can be used to in the treatment of cancer. Furthermore, it is still unclear whether the inhibition of Aurora A and/or Aurora B, could be advantageous in terms of providing therapeutic benefit in oncology (Keen and Taylor, 2009).

The contestation surrounding the activity of aurora kinase inhibitors may account for the relatively large number of publications found to mention aurora B<sup>72</sup> which, prior to the

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[www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1936](http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1936) (accessed 15/5/2015).

<sup>72</sup> Search term used: ("aurora B" OR "aurora 1" OR "aurora-B" OR "aurora-1") AND ("1900/01/01"[Date - Publication]: "2005/31/12"[Date - Publication])

year barasertib entered clinical trials (2005) amounted to 157 articles from a PubMed search.

The mitotic paradigm for understanding the mechanism for the anti-cancer activity of barasertib was suggested in a 2009 publication (Keen and Taylor, 2009). This article hypothesises that a reduced toxicity of targeted anti-mitotic agents<sup>73</sup> could be inferred through the inhibition of mitotic spindle assembly, without interfering with microtubules in non-dividing cells (ibid). Furthermore, despite a focus on the aurora A kinase in initial aurora kinase interest, due to its overexpression in colon cancer, it was the aurora B kinase target for which most of the initial clinical candidates were found (Keen and Taylor, 2009). This highlights a lack of alignment between the understanding of target-disease interaction and drug-target activity.

Despite the acceptance of the mitosis paradigm for aurora kinases, uncertainty remained. Further molecular biology investigations into the mechanisms of aurora B kinase inhibitors highlighted that, rather than acting as anti-mitotics, they drive mitosis whilst interfering with the mechanics of cell division (Keen and Taylor, 2009). This alternative perspective did ultimately contribute towards the same conclusion, that inhibiting aurora kinases should have led to cell death, however it illustrates that the uncertainty over barasertib's mechanism of action persisted through early stage trials.

In preclinical trials barasertib showed “striking *in vivo* activity” with *in vitro* studies showing the prevention of cell division through chromosome misalignment (Mortlock et al., 2007). Furthermore, barasertib showed phase II response rates ranging from 20% (Collins et al., 2015), with an additional 33% of patients showing a stable disease to 25% response rates (Lowenberg et al., 2011). This is comparable to pazopanib which achieved a response rate of 30% in its phase III (Sternberg et al., 2009) and nelarabine which showed 55% (Berg et al., 2005) and 41% (Hernandez-Ilizaliturri and Czuczman, 2009)).

In addition, toxicity levels of barasertib did not offer substantial benefits over other anti-mitotics (Keen and Taylor, 2009), highlighting its inadequacy in comparison to established anti-cancer cytotoxins. Indeed, Keen and Taylor (2009) describe the drug as both encouraging, in responses, and disappointing, in toxicities.

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<sup>73</sup> The types of toxicities seen in other anti-mitotic agents came from the interaction of the drug in non-dividing cells leading to a loss of sensation in patients' extremities.

The disappointment in barasertib toxicity, however, was not reflected in others' efforts. In a recent review (2011-2013) there were at least 3 ongoing post-phase II aurora kinases in development<sup>74</sup> and a broad range of patents<sup>75</sup> (Cheung et al., 2014). However, the rate at which patents associated with aurora kinases was observed to have seen a decline when compared to previous years, although journal articles remain on the rise (ibid).

It is also relevant to consider the knowledge base surrounding AML, as the barasertib primary indication. AML was relatively well researched prior to the barasertib trials<sup>76</sup>, represented in the large number of publications found to mention the disease subtype (31,207<sup>77</sup>). This indicates that, despite the lack of knowledge of the target-disease interaction and target-based knowledge, the understanding of the disease was advanced.

This section has highlighted the barasertib knowledge base and the development of understanding in a group of novel targets, namely aurora kinases. It has demonstrated a shift from a rhetoric around 'oncogene' to an appreciation of role of the target in mitosis. The technological uncertainty during this time, although not inhibitory to the continued use of this target in the quest for anti-cancer targeted therapies, was a factor in the development of barasertib<sup>78</sup>. This justifies the designation of this case as representative of full non-membership into the set for extensive and accumulated knowledge base.

#### **6.3.4 Market demand (QCA score = 0)**

Barasertib was tested in a range of tumour types in early stage development. Preclinical studies were undertaken in human colon, lung and hematologic tumour xenografts in immunodeficient mice (Wilkinson et al., 2007). The intention to develop the drug for a broad range of indications is further confirmed by AZ in their annual reports from 2004-2007 which state that barasertib is in development (from preclinical through to phase I)

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<sup>74</sup> These were danusertib by Nerviano Medical Sciences, alisertib by Millennium and ENMD 2076 by CASI Pharma, formerly EntreMed

<sup>75</sup> Patents held by Ambit Biosciences Co, Amgen, Boehringer Ingelheim, Cancer Research Technology, Genosco and Oscotec Inc., Guangzhou Institute of Biomedicine and Health, Chinese Academy of Science, Merck, Moffit Cancer Centre, Nihon University (Japan), National Health Research Institutes, Sanofi, Shenzhen Salubris Pharma Co and Shanghai Institute of Pharma Industry, Sun Yat-Sen University and Sunshine Lake Pharma Co

<sup>76</sup> Taken up to and including 2005.

<sup>77</sup> This figure was obtained using the Medical Subject Heading (MeSH) term 'Leukemia, Myeloid, Acute' as a search term in PubMed.

<sup>78</sup> This is also linked to the increased tendency to provide data on the mechanism of action of a drug in the New Drug Application to the FDA (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm176522.htm>)



for solid tumours and haematological malignancies (AstraZeneca PLC, 2004, AstraZeneca PLC, 2005, AstraZeneca PLC, 2006, AstraZeneca PLC, 2007, Boss et al., 2011). It is not uncommon in early stage trials for cancer drug development to be broad ranging.

However, an additional phase I trial indicates that AZ were considering AML specialisation for barasertib development (Tsuboi et al., 2011, Dennis et al., 2012, Kantarjian et al., 2010, Miyawaki et al., 2010). In 2008/9 the AML focus continued with a phase II/III trial, however, AZ annual reports still projected potential for a broader drug application to haematological malignancies (Pharmaprojects, AstraZeneca PLC, 2008, AstraZeneca PLC, 2009).

Despite AML affecting only a small patient population, it is an area of severe unmet need with stem cell transplants<sup>79</sup> and conventional chemotherapy (i.e. cytotoxic drugs) providing the main treatment option. This implies a large potential return if barasertib had been successful as it would have been the first targeted therapy to be approved in this area. A competitor, gemtuzumab was approved in 2000, providing an established treatment for AML patients prior to the initiation of development of barasertib<sup>80</sup>.

This relatively narrow therapeutic focus of the development barasertib pursued by AZ, and a competitor in the AML market, indicates a small potential market demand for barasertib. This may have contributed towards the termination of the project which was reported to be for economic reasons. These have been taken as contributory factors in the justification of the QCA score as '0' i.e. full non-membership into the set of high market demand.

### **6.3.5 Stakeholder Perspectives (QCA score = 0)**

The characterisation of the drug as an oncogene, early on in its development, would have contributed towards the expectations that surrounded its development. As discussed in Chapter 2, throughout the late 1980s and 1990s, the oncogene approach was perceived as a promising avenue for cancer therapeutics by the scientific and

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<sup>79</sup> Stem cell transplants are extremely similar to bone marrow transplants but differ in the way in which the stem cells are obtained.

<sup>80</sup> This scenario presents a more significant competitor than was seen to be the case in pazopanib where the competitor molecule was developed when the drug was in phase III, indicating a race to market.

industrial community. This trend is noted by Fujimura (1988), who describes the concept of 'oncogenes' as a 'bandwagon'.

In addition, aurora kinases were met with high expectations in the early 2000s demonstrated in the publication and analysts report entitled: 'Aurora Kinase inhibitors – the dawn of a new approach' (Research and Markets, 2005). However, this report highlights the aforementioned debate around the limited understanding of the selectivity of aurora kinase inhibitors, and the extent to which mitotic damage may arise (Research and Markets, 2005).

Mentions of barasertib by stakeholders in the media are non-existent. It would be expected that there would be strong support for the development of a drug in an area of unmet need; however, it is not apparent that AZ or other stakeholder publicly recognised this during barasertib development

This evidence shows a lack of positive stakeholder perspectives for barasertib, despite the hype that may have come from the classification of the drug as an oncogene. This justifies the QCA score of '0' (i.e. full non-membership into the group positive stakeholder expectations).

### **6.3.6 Organisational environment (QCA score = 1)**

Barasertib was an output from an AZ-SUGEN collaboration. SUGEN were a US-based biopharmaceutical company focused on the discovery and development of small molecule drugs targeting cellular signalling pathways (SUGEN, 1996). The agreement between AZ and SUGEN, for the licensing of five SUGEN-discovered small molecule kinase inhibitors (of undisclosed identity at the time), was signed in 1995. The agreement specified the responsibility of SUGEN for performing target identification, target validation, assay development and screening for initial leads, while Zeneca undertook lead identification/optimization and preclinical/clinical development activities (Zeneca Group, 1995, SUGEN, 1997). Zeneca made a \$12.5m equity investment in SUGEN as part of the collaboration, in addition to a previous investment of \$7.5m, in the SUGEN initial public offering, and a \$5m technology set-up fee (ibid). When SUGEN was acquired by Pharmacia & Upjohn in 1999, AZ had an equity stake of 20% in the firm (AstraZeneca PLC, 1999b).

The 1995 agreement outlined that SUGEN gained the right of first negotiation for Zeneca cancer drug candidates that did not reach the minimum market size required for internal clinical development (Zeneca Group, 1995). This implies that even if the drug does not have sufficient commercial potential for Zeneca, it might be acceptable to SUGEN,

demonstrating the difference, previously highlighted in section 3.4.1, in the notion of adequate market expectations, between small firms and large firms. For instance, smaller firms have smaller pipelines and therefore less choice about which products they produce and, conversely larger firms can be more meticulous but also have larger overheads to account for, thereby demanding higher profit margins.

Furthermore, this term of the agreement also illustrates how a small biotech firm can be left with the discarded small-market projects from big pharma. This term of the agreement did not benefit the development of barasertib, despite AZ stating that development was discontinued for economic reasons, because the agreement was only valid for five years (to 2000), by which time SUGEN had been acquired by Pharmacia & Upjohn (1999) (AstraZeneca PLC, 1999b).

The AZ strategy (in oncology and kinase inhibitors) witnessed shifts during the development of barasertib (1995-2011). This is illustrated in the AZ press release announcing the SUGEN-Pharmacia acquisition: 'AstraZeneca is currently number two in oncology and aims to become the leading pharmaceutical company in this area' (AstraZeneca PLC, 1999b). This press release also claims that AZ has capabilities to continue developing kinase inhibitors without future SUGEN collaboration, as Les Hughes, AZ Global Head of Cancer Research states:

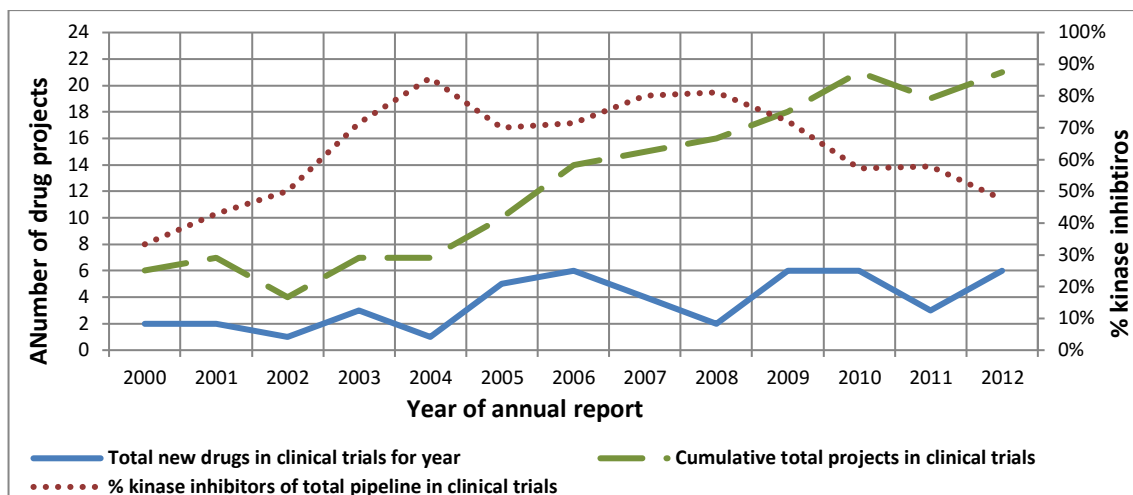
"We have had a friendly and productive research relationship with SUGEN for the past four years. The collaboration has augmented the work AstraZeneca has carried out on its own kinase target research programs and has broadened the opportunities available to us. We now have a strong in-house presence in this technology with good options to pursue our work in this important research area." (AstraZeneca PLC, 1999b).

AZ also describe the expansion of their oncology R&D pipeline in their 1999 Annual Report:

'Building its successful endocrine treatments, AstraZeneca is committed to further development of both endocrine and cytotoxic products and to a number of 'novel approaches'<sup>81</sup>, including anti-proliferates, anti-angiogenics and inhibitors of cancer invasion, to combat prostate, breast, colorectal, lung, gastric and other cancers.' (AstraZeneca PLC, 1999a)

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<sup>81</sup> In this quote barasertib would come under the umbrella of 'novel approaches'.



**Figure 7 Graph showing AZ changes in oncology pipeline. Right hand axis indicates % of kinase inhibitors (% of total pipeline in clinical trials); left hand axis indicates number of projects (both total new drugs in clinical trials for year and cumulative total project in trials).**

YEAR	'99	'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12
Kinase inhibitor projects in trials	1	2	3	2	5	6	7	10	12	13	13	12	11	10
Total new drugs in trials for year	4	2	2	1	3	1	5	6	4	2	6	6	3	6
Cumulative total projects in trials	4	6	7	4	7	7	10	14	15	16	18	21	19	21
Non-kinase inhibitors in trials	3	4	4	2	2	1	3	4	3	3	5	9	8	11
% kinase inhibitors of development pipeline	25%	33%	43%	50%	71%	86%	70%	71%	80%	81%	72%	57%	58%	48%

**Table 16 Analysis of AZ Oncology pipeline. Data taken from AZ annual reports**

Looking into the AZ oncology pipeline we observe these large increases in the numbers of drugs year on year (see Figure 7 and Table 16) indicating an increase in interest in oncology product in general. Furthermore, we also observe a peak in the proportion of products categorised as kinase inhibitors, including barasertib, during the period 2004-2010. Specifically we see an increase from 33% and 43% in 2000 and 2001, peaking to 86% in 2004 and 81% in 2008, returning to 48% in 2012 (see Table 16). Significantly for barasertib, the 2004 and 2008 peaks of kinase inhibitors correspond with the time prior to the project entering trials (2004) and the year prior to the initiation of phase II trials.

This implies that barasertib development was part of a larger strategy for kinase inhibitors and oncology drugs. This indicates that the development of barasertib was part of a firm-wide oncology and kinase inhibitor strategy.

This section has demonstrated a shift at AZ towards targeted oncology therapies, including aurora kinases. Although the project was subject to a collaboration, which may have implied knowledge transfer difficulties, this took place in the early stages of barasertib development and led to the adoption of the relevant capabilities by AZ. These factors contribute towards the conclusion that the development of barasertib is characterised by a relatively unproblematic organisational environment, and therefore the case shows full membership into the set for supportive organisational environment ('1').

### **6.3.7 Barasertib Conclusion**

Through the progression of barasertib, issues and costs gradually accumulate, both leading to drag cost and project drag. This contributed towards increasing scrutiny and pressure on development of the drug, accounting for the termination of the project despite comparable efficacy, and justifies the statement by AZ that they discontinued barasertib development for economic reasons.

In this case history we see a project that was embedded in a rhetoric of oncogenes that was used as a tool to generate support however there was disappointment associated with an incomplete understanding of the drug's mode of action. As knowledge accumulated around barasertib there was also a realisation that the potential market demand was not as broad as initially thought. In addition, the lack of stakeholder recognition of the project did not provide any support to offset the accumulating project drag.

## **6.4 Nelarabine –Influence of a Champion**

In contrast to the cases seen before the nelarabine case demonstrates how issues that could be detrimental to the outcome of a project are resolved. This differs from pazopanib which progressed without problems, and barasertib in which the project did not benefit from mechanisms to overcome project drag.

Nelarabine (506U, arranon, atriance, GW506U78, nelzarabine) was the subject of an established research stream spanning decades, developed by Burroughs Wellcome (BW) (subsequently GW and GSK), and indicated for T-cell lymphomas and leukaemias. The project suffered from a range of issues including: 1) low market potential, 2) strategic fit issues, i.e. how well nelarabine fitted with the priorities of GSK and the industry, and 3)

management and other difficulties following large scale mergers. A consistent research group, the action of a key individual and a strong clinical response in an area of unmet need are shown to be key in overcoming these issues and lead to the eventual launch of the project, successfully overcoming the observed drags on the project.

#### 6.4.1 Interview sources

This case history is informed by email correspondence, referred to as 'email correspondence W'.

#### 6.4.2 Introduction

Nelarabine is a prodrug of guanine arabinoside (ara-G) activated in the presence of adenosine deaminase. The project was discovered at BW, in collaboration with researchers at Duke University, developed by GSK (after the various mergers) and approved by the FDA for the treatment of Acute Lymphoblastic Leukaemia (ALL) in 2005.

<b>1984</b>	Ara-G found to be selectively toxic against T-leukaemic cells
<b>1988</b>	Elion and Hitchings win Nobel Prize
<b>1994</b>	Nelarabine Phase I trials initiated at Duke University and University of North Carolina supported by BW
<b>1995</b>	Glaxo and BW merged
<b>1997</b>	Nelarabine Phase II study initiated (children and young adults)
<b>2000</b>	SmithKline Beecham merge with Glaxo Wellcome
<b>2002</b>	Additional Phase II trials undertaken (adults)
<b>2003</b>	Fast track status granted to nelarabine
<b>2005</b>	Orphan Drug Status granted; Nelarabine approved

**Table 17 Key events in development of nelarabine**

#### 6.4.3 Knowledge base (QCA score = 1)

Nelarabine originated in the laboratory of the Nobel Prize winners George Hitchings and Gertrude Elion<sup>82</sup> at BW in Tuckahoe New York, USA (later Research Triangle Park). This research group was mainly focused on the therapeutic application of purine analogues<sup>83</sup>, synthesising more than 100 purine analogues by the early 1950s including the first

<sup>82</sup> Hitchings and Elion (along with James Black) jointly won the Nobel Prize in Physiology or Medicine in 1988 ([http://www.nobelprize.org/nobel\\_prizes/medicine/laureates/1988/elion-facts.html](http://www.nobelprize.org/nobel_prizes/medicine/laureates/1988/elion-facts.html))

<sup>83</sup> Recall Chapter 2 (section 2.2.5.3) discussion of purine analogues developed by Hitchings and Elion at Burroughs Wellcome.

cytotoxic analogues active in leukaemia, 6-mercaptopurine (6-MP), (Academy of Achievement, 1991).

Synthesis of ara-G was first published in 1964 (Reist and Goodman, 1964), however clinical use was limited due to inadequate solubility proving a major obstacle to drug development (Kisor, 2009, Hernandez-Ilizaliturri and Czuczman, 2009). In response to this, the BW research group pursued the more soluble prodrug of ara-G, 506U (nelarabine) (ibid). Lab experimentation of ara-G as a therapeutic product was facilitated by the enzymatic synthesis of ara-G, published in 1981 (Krenitsky et al., 1981, Kisor, 2009). In the early 1980s the selective toxicity against T-leukaemic cells, implies the potential to use ara-G as an anti-leukaemic agent (Lambe et al., 1995).

Running in parallel to the work on ara-G was research at Duke University, undertaken by Joanne Kurtzberg, in which a murine model of T-cell leukaemia/lymphoma was being developed (email correspondence W). This model was later used for preclinical testing for ara-G, when Elion had the idea of giving a sample of ara-G to Kurtzberg to test it (email correspondence W). Having demonstrated responses in T-cell leukaemic murine models (Gravatt et al., 1993), the key challenge of using ara-G as a therapeutic remained the drug's poor water solubility, stimulating the suggestion that a prodrug approach might be more suitable (Lambe et al., 1995).

Preclinical studies of 506U in cynomolgus monkeys showed rapid conversion to ara-G, demonstrated in high plasma levels of the compound, with results replicated in immunodeficient mice (Lambe et al., 1995). As demonstrated in clinical experience of other nucleosides, this was shown to be an important indicator of clinical efficacy (ibid).

In response to positive preclinical results, an IND was submitted proposing the initial (Phase I) study in patients with refractory haematological malignancies (Kisor, 2009). In addition a patent was filed, published in 1996 (Krenitsky et al., 1996a) covering the use of ara-G derivatives to treat T-cell leukaemia.

Trials began in 1994, 30 years after the initial synthesis of ara-G (Kisor, 2009). The first study was undertaken at Duke University and University of North Carolina, supported by BW. This trial was later expanded to include patients at the Boston University Medical Centre and the MD Anderson Cancer Centre (ibid). This study determined maximum tolerated dose, toxicity profile, and pharmacokinetics of nelarabine in 93 paediatric and adult patients with refractory haematological malignancies. T-cell ALL and T-cell lymphoblastic leukaemia patients (39 in total) showed 9 (23%) complete responses, and an additional 12 (31%) partial responses (Kurtzberg et al., 2005). Another phase I trial

showed 5 complete responses from a total of 28 patients with T-ALL or T-LBL (Hernandez-Ilizaliturri and Czuczman, 2009). It was these 'dramatic responses' in an indication that was otherwise unresponsive to standard treatment that motivated further development of nelarabine (email correspondence W).

One published phase II trial treated 16 patients (peripheral T-cell lymphoma, or low grade B-cell lymphoma). Of the 11 that were evaluable, 2 showed a complete response, and 4 a partial response (Kisor, 2005). Another published phase II trial undertaken in children and young adults showed a 55% response rate from 106 patients (Berg et al., 2005). In 39 evaluated patients with relapsed/refractory T-ALL/T-LBL 41% showed clinical responses with 31% showing complete responses (Hernandez-Ilizaliturri and Czuczman, 2009). In conclusion phase II trials showed that nelarabine was efficacious, however dose-limiting toxicities were also identified (ibid).

Nelarabine was approved for fast track status in 2003 and Orphan Drug Status in 2005. Furthermore, trials supported the approval of nelarabine, in 2005 (FDA) and 2007 (EMA), for treatment of T-ALL and T-LBL.

The knowledge base supporting nelarabine development is also embedded in the publications concerning the disease for which the drug was primarily developed. For lymphoid leukaemias a large number of articles (29,200<sup>84</sup>) were published in the years preceding nelarabine trials (up to and including 1994). This high level of knowledge is also supported by the observation, made in Chapter 2, that haematological malignancies are the best understood cancers due to the ease of research in this area.

In addition to the growth of the knowledge base during the development of nelarabine, the consistency of the research team involved also contributed towards the accumulation of this knowledge, which will be discussed in more detail below.

In summary the knowledge base for nelarabine is a long established stream with GSK contributing a consistent research group throughout trials. This suggests that the project was based on a substantive evidence base that contributed towards straightforward

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<sup>84</sup> This figure was obtained using the Medical Subject Heading (MeSH) term 'leukemia, lymphoid' as a search term in PubMed. This is the term generated to account for Acute Lymphocytic Leukemia, and includes the subsets: 'Leukemia, B-Cell; Leukemia, Biphnotypic, Acute; Leukemia, Polymphocytic; Leukemia, T-Cell; and Precursor Cell Lymphoblastic Leukemia-Lymphoma.



clinical development. This was despite the emergence of patient toxicity in trials, which would be partially expected in a non-targeted therapeutic such as nelarabine.

#### 6.4.4 Market demand (QCA score = 0)

The primary indication for which nelarabine was developed was T-cell ALL, a rare haematological malignancy. All published phase I trials for nelarabine were for haematological malignancies (Kisor et al., 2000, Kurtzberg et al., 2005, Kurtzberg et al., 1996, Kisor, 2005), with the exception of one that was in leukaemia (Gandhi et al., 2001),.

This shows specialisation of nelarabine from early development, a strategy that is rare in pharma drug development. Haematological therapeutics are relatively straightforward to develop due to the ease of assessment of a drug's activity, using blood-based biomarkers, and the practice of using haematological cancer models for research purposes (as mentioned in Chapter 5). However, it is likely that the haematological focus for nelarabine came from the finding, in the 1980s, that ara-G had T-cell specificity (Lambe et al., 1995).

Further trials indicated a specialisation of nelarabine in T- and B-cell lymphomas and leukaemias, including ALL (De Angelo et al., 2002, Kisor, 2005), lymphoblastic leukaemia (De Angelo et al., 2002), B-cell or peripheral T-cell lymphomas (Thompson et al., 2005, Goy et al., 2003) and non-Hodgkin's lymphoma (Kisor, 2005, Goy et al., 2003, Berg et al., 2005).

Although this is a long list of indications (as illustrated in Table 18) all of these represent small patient populations, with the exception of non-Hodgkin's lymphoma which is comparable to urinary bladder cancer incidence. In fact, it is only when combining the incidence of all leukaemias and lymphomas (in the USA) that incidence is comparable to larger indications such as breast cancer, where the former is less than half of the latter.

Indication	Incidence (estimated new cases in US)	Deaths (estimated in USA)
Acute Lymphoblastic leukaemia	6,250	1,450
Non-Hodgkin's Lymphoma	70,800	19,790
Leukaemias and Lymphomas	137,170	45,390
Breast Cancer	234,190	40,730
Urinary Bladder Cancer	74,000	16,000

**Table 18 Summary of epidemiology statistics for relevant cancer subtypes<sup>85</sup>**

<sup>85</sup> [www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf](http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf)

Despite being indicated for a relatively small population, industry analysts forecasted the project to have peak annual worldwide sales of US\$1bn, characterising it as a 'blockbuster' (Pharma Marketletter, 2005c). Patient size associated with nelarabine at this time was quoted to be 1,600 adults and children for T-cell ALL or T-cell lymphoblastic leukaemia. Due to this subtype of leukaemia being an unmet need (email correspondence W) afflicting children<sup>86</sup>, it is likely that the high projected nelarabine sales stemmed from the potential for high prices to be expected from this target market. However, we will take sales estimations tentatively due to the widespread introduction of tight pricing controls<sup>87</sup>, implying this is a risky strategy.

Nelarabine development took continued for a long period, however, this did not imply patent-related appropriability issues due to the filing of patents in 1993 (Krenitsky and Porter, 1995), followed by 1994 (Krenitsky et al., 1996b), 1995 (Krenitsky et al., 1998a, Krenitsky et al., 1998b, Krenitsky and Porter, 1996) and 1998 (Averett et al., 1998). This indicates that patents would not be expected to expire until around 2018.

Despite the reported potential for this drug to reach high prices and therefore sales revenue, we observe that this is not guaranteed due to pricing controls. In addition, the specialisation of the drug to specific types of leukaemias and lymphomas which largely present a small potential patient population, indicates a small expected market demand for the drug. Therefore, this drug should be scored (for QCA) in line with non-membership into the set for high market demand (i.e. '0').

#### **6.4.5 Stakeholder Perspectives (QCA score = 0)**

In 2003 media mentions of nelarabine begin. One of the first of these is in the GSK R&D Meeting for Analysts and Investors when the drug is described as a 'done deal' and a 'very interesting product for some of the T-cell leukaemias', despite approval being two years away (GlaxoSmithKline plc, 2003). This feeling is echoed in the move to obtain fast track drug status from the FDA in 2003. The positive perception of the project

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<sup>86</sup> [www.cancer.org/cancer/leukemiainchildren/detailedguide/childhood-leukemia-how-classified](http://www.cancer.org/cancer/leukemiainchildren/detailedguide/childhood-leukemia-how-classified)

<sup>87</sup> Although outside the scope of this thesis, pricing controls are a controversial issue in drug development and marketing. Here, in 2004 the US Department of Commerce, International Trade Administration studied 11 OECD countries and found that all implement some initiative for pricing controls, whereby often the rationale behind the determination of drugs sales prices were not disclosed even to the pharmaceutical firms developing them (<http://www.ita.doc.gov/td/chemicals/drugpricingstudy.pdf>). Therefore, as a rule in this thesis we do not consider potential high price as a contributor to expected market demand.

continued in a GSK Earning Conference Call in 2004, when the results for nelarabine are described as 'very impressive' (GlaxoSmithKline plc, 2004).

However, expectations from the GW side had not always been positive. GW intended to discontinue the development of the project, passing manufacturing responsibility over to the Cancer Therapy Evaluation Program and the NCI, subsequent to the Wellcome/Glaxo merger (email correspondence W). While the NCI were enthusiastic about the effect the drug was having in leukaemia patients, it was the low market potential that prompted a waning of excitement from the GW perspective (this issue will also be revisited in the next section).

Nelarabine development had limited coverage in mainstream press, only appearing briefly prior to approval (Tomlinson, 2004). Other mentions of nelarabine in the media (press releases and GSK pipeline reports) focus on trial results and reports of approval.

Nelarabine was a drug developed for a very rare cancer indication that mainly affected children. One of the aspects of developing drugs in this area is the difficulty in patient recruitment. This is described, alongside the toxic side effects, as one of the major difficulties in the development of nelarabine (Hernandez-Ilizaliturri and Czuczman, 2009). In addition, the acute nature of the disease, with fast tumour growth and the high rates of relapse added to the complexity in finding and treating patients (Hernandez-Ilizaliturri and Czuczman, 2009). However, these considerations, of the focus on children and an area of unmet need, are expected to have been met with support from patients and clinicians, although this is not observed in media reports. In addition, this contributes to the ability for the drug to demand orphan drug status and fast track approval.

This section indicates that within the firm, perspectives around the product were mixed. Impressive results were described as well as the project being a 'done deal', however, the project was almost shelved during the merger between Glaxo and Wellcome and evidence for a lack of media coverage was found. The threshold for a supportive stakeholder response is therefore not deemed to have been met (QCA score = 0).

#### **6.4.6 Organisational environment (QCA score = 1)**

There are several aspects of the organisational environment that facilitated the successful development of nelarabine, justifying the QCA score of '1'. The first of these is the consistent and supportive network of people working on the project. As mentioned, early development of nelarabine was undertaken at BW in the lab of Nobel Prize winners Hitchings and Elion.

Despite the lab being part of a big pharma firm, in an interview Elion describes an academic, nurturing and positive organisational culture:

“Burroughs Wellcome is a very unusual company ... It was the vision of Henry Wellcome that this would be a research organization, and it would make its money by selling pharmaceuticals, and that money would go back into research. Our research lab grew very rapidly as we began to be successful. The money did go back to research. Some of it went to our research; some of it went to other people's research, via the Wellcome Trust... But on the whole, the idea was to do research, find new avenues to conquer, new mountains to climb... It [Burroughs Wellcome] was a place where you could do good work. People wouldn't be looking over your shoulder saying, “What have you done for me lately?” (Academy of Achievement, 1991)

Encouraging ‘undirected research’ to nurture ‘fundamental curiosity’ facilitates a cooperative working environment both within the firm and in collaborative relationships. In particular, cultural barriers in academia-industry linkages are broken down facilitating interaction and knowledge transfer.

The positive culture at BW at the time has also been highlighted in a series of interviews with the former top management of the company, undertaken by Wellcome (Wellcome Collection). Here former President of BW, Fred Coe, describes the 1950s and 1960s firm as being small, focused on early stage research and driven by pharmacists (Wellcome Library, 2001b). This is further highlighted by Bill Sullivan who describes Wellcome as “traditional”, “family oriented”, with “nice people working for it” and a laissez faire attitude (Wellcome Library, 2001d). It was not until the move to Research Triangle Park, from Tuckahoe, New York, that BW really grew and expanded.

Furthermore, despite being a private organisation, until 1986 when the firm began floating shares on the stock market, the entirety of the firm was owned by the Wellcome Trust<sup>88</sup> allowing for a non-commercial focus and the reinvestment of profits back into research (Wellcome Library, 2001d). However, this became problematic when the company wanted to initiate trials, whereby the scale of funds needed were unavailable and a collaboration with Sloan Kettering was undertaken to fill the gap (Wellcome Library, 2001c, Wellcome Library, 2001b).

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<sup>88</sup> [www.wellcome.ac.uk/Investments/History-and-objectives/Investments-history/](http://www.wellcome.ac.uk/Investments/History-and-objectives/Investments-history/)

The freedom of the researchers at BW, and the status of Elion and Hitchings as respected by the scientific community, supported the development of an academic culture at BW in the years from the 1950s, up until the Glaxo/Wellcome merger in 1995 (Wellcome Library, 2001c, Wellcome Library, 2001a). Hitchings and Elion had wide networks and the organisation had close relationships with academic laboratories (Wellcome Library, 2001c, Wellcome Library, 2001b).

The organisational culture and the location of BW (and later GSK) at Research Triangle Park, also helped to encourage collaborations throughout the nelarabine development. One commentator emphasises the importance of collaborations to the success of the project:

‘only through a sustained collaboration of industry, academia, and government were the clinical data produced to demonstrate that the drug has a role in treating certain rare forms of leukemia and lymphoma when patients have exhausted standard treatment options’ (Koenig, 2006).

This is significant due to the common difficulties associated with inter-organisational collaborations, particularly between industry and academia, where different institutional cultures, expectations and objectives can be problematic (Bstieler et al., 2015).

These collaborations were consistent throughout the development of nelarabine and involved a core team of investigators at a range of institutions, including: Elion and Krenitsky from BW, Kurtzberg from Duke University, Kisor from Ohio Northern University, Berg from the Texas Children’s Cancer Center at the Baylor College of Medicine, Gandhi, Keating and Plunkett from the MD Anderson Cancer Center and Mitchell from the University of North Carolina (Krenitsky et al., 1981, Lambe et al., 1995, Kurtzberg et al., 1996, Gandhi et al., 1998, Kisor et al., 2000, Gandhi et al., 2001, De Angelo et al., 2002, Berg et al., 2003, Berg et al., 2005, Kurtzberg et al., 2005, Kisor, 2005, Kisor, 2009).

In addition Gertrude Elion ‘started the ball rolling’ for nelarabine and had particular interest in nelarabine after her retirement and until the end of her life in 1999 (Koenig, 2006). Here Koenig, who worked at GSK, comments: ‘one reason Elion kept coming back was to champion nelarabine’, associated with issues facing development such as side effects, patient recruitment and weighing ‘medical and commercial potential against the opportunity of other drugs in the pipeline’ (Koenig, 2006).

Elion was an experienced researcher involved in the development of many ‘successful’ drugs throughout her career. She has been described as having a ‘direct manner’ and

being ‘wholly unpretentious’ (Koenig, 2006) and as a good networker, a diplomat, and “warm person” (Wellcome Library, 2001c).

Elion continued to be involved in the drug development process at BW (later GW) until her death in 1999 despite retiring after winning the Nobel Prize (Wellcome Library, 2001c). She professes that after her official retirement she ‘tried to take an active part in the discussions, seminars, and staff meetings relating to research’ at the firm (Elion, 2006). Furthermore, Elion’s network, as Research Professor of Medicine and Pharmacology at Duke University, was key to the development of nelarabine facilitating the involvement of Kurtzberg in nelarabine’s development.

Elion was a decisive factor in contributing towards nelarabine’s success (email correspondence W). This was linked to the level of influence of Elion as a champion, facilitated by achieving the Nobel Prize (email correspondence W). In addition, her role, until her 1983 retirement, as the Head of the Department of Experimental Therapy (Elion, 2006), is likely to have contributed towards her influence as a key individual in nelarabine’s development. The consistency of the research team and the presence of a ‘champion’ for the project may also have helped in overcoming the difficulties caused by the mergers occurring during nelarabine development, firstly in 1995 when BW merged with Glaxo to create GW, which then went on to merge with SKB in 2000 to form GSK (email correspondence W).

The discontinuities caused by these mergers are demonstrated in the media. Firstly, in September 1995 when GW were reportedly cutting 7,500 jobs worldwide as a cost saving strategy (Grimond, 1995b), whilst increasing research spending and productivity of R&D operations (Grimond, 1995a). Secondly, the Glaxo/BW merger led to a loss of many people working at Wellcome, as Dr Howard Shaeffer (former VP Research, Development and Medical) puts it: “I was really surprised that Glaxo didn’t keep more of the Wellcome people, BW people... that really was the end of the BW company, when Glaxo took over” (Wellcome Library, 2001a).

One review reflects that subsequent to the merger, GW made a firm commitment to formally sponsor the development of nelarabine, a decision reportedly based on the ‘clear therapeutic need’ for patients suffering from T-cell haematological malignancies (Kisor, 2009).

However, this period was also associated with some reticence to develop nelarabine, whereby GW refused to continue development of the drug (email correspondence W). This may have been down to the differences in organisational cultures between the

former BW and the enlarged organisation whereby Krenitsky describes: “The drug creates its own market... They [Glaxo] didn’t have that vision” (Wellcome Library, 2001c). This highlights that while Burroughs Wellcome were scientifically-oriented and focused on producing effective drugs for unmet needs, Glaxo were more commercially oriented.

This section has demonstrated that the supportive networks of investigators involved in nelarabine development had a positive impact on the success of the project. It is also fair to conclude that this consistency, on an individual-level, also helped insulate the development of nelarabine from the potential detrimental impact that mergers could have had on the project.

This section has highlighted a positive organisational environment surrounding the development of nelarabine, despite strategic fit issues and the major merger events that took place. Here, the action of key individuals and the organisational culture of the firm early on in the drug’s development, contribute towards the membership of the case into the condition supportive organisational environment (QCA score = 1).

#### **6.4.7 Nelarabine Conclusion**

The development of nelarabine faced four clear issues including: duration of development, strategic fit, low market potential and organisational disruption from large scale mergers. These contributed towards the accumulation of project drag, however the case history has demonstrated how the action of three key mechanisms contributed towards overcoming these issues.

The consistency of the research group and the presence and influence of a key individual were key to facilitating an established and accumulated knowledge stream, prior to the synthesis of nelarabine. We can assume that a consistent research group contributes towards the development of routines that benefit innovation. In addition, characteristics of Elion as a key individual, such as her influence (contributed towards by her experience, personality and Nobel Prize), network and persistent involvement in nelarabine development influenced its success. In this Elion took on more than one key individual role (e.g. inventor, organisational sponsor, business innovator and technological gatekeeper) again highlighting the importance of her involvement in the project.

These mechanisms also contributed towards overcoming the organisational and knowledge transfer difficulties associated with mergers and collaborative agreements. Indeed, when GSK wanted to discontinue development it was the action of the product champion that motivated its continued development.

Despite the project taking over two decades to be developed, the BW research laboratory had similarities to an academic lab, facilitating not only the transferral of expertise and tacit knowledge, and the integration of disciplinary approaches, but also the learning between the academic and industrial teams. Furthermore, the pronounced clinical response seen in an area of unmet need highlights a potential strategy in drugs with low market potential.

## **6.5 Plevitrexed – Strategies, Patents and Inter-Organisational Work**

One project that was also not successfully carried forward to approval phases, from big pharma, was plevitrexed (ZD9331). This project is comparable to nelarabine due to the collaborative environment in which it progressed.

Plevitrexed was discontinued due to a culmination of issues throughout the course of its development (project drag). Discontinuation of the drug resulted from delays in project development leading to appropriability (patent) issues and an unsuccessful licensing effort when AZ terminated the license, and it reverted to BTG<sup>89</sup>. These delays may be associated with the collaborative environment of the project. The project also suffered from insufficient efficacy in patients coupled with a lack of strategic fit at AZ.

### **6.5.1 Interview sources**

Two interviews were undertaken to supplement the publicly available data collected. The first with an investigator directly involved in the development of the thymidylate synthase inhibitors, interviewee J. In addition, reflections interviewee C and L, and email correspondence X are also drawn upon.

### **6.5.2 Introduction**

Plevitrexed is a small molecule anti-folate thymidylate synthase inhibitor developed primarily for gastric cancer, as a result of a research collaboration between the Institute of Cancer Research (ICR) and AstraZeneca (AZ), with support from BTG. The project began initial clinical development in the 1990s, on the back of raltitrexed, a previously approved drug. The project was partnered with AZ until 2002, when they discontinued development and British Technology Group (BTG) licensed the compound, seeking a development and commercialisation partner for the drug.

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<sup>89</sup> Although BTG were not actively involved in the ICR/AZ collaboration they did support early work on raltitrexed (the precursor to plevitrexed) and therefore shared the IP with AZ.



**Table 19 Key events in the development of plevitrexed**

<b>1940</b>	Sidney Farber begins work on anti-folates in cancer therapeutics
<b>1947</b>	Aminopterin (first anti-folate) first used in cancer therapy
<b>1979</b>	ICR work on anti-folates begins
<b>1991</b>	Raltitrexed Phase I begins in Europe
<b>1993</b>	Raltitrexed Phase III begins
<b>1996</b>	Plevitrexed Phase I trial initiated; Raltitrexed approved for colorectal cancer
<b>1998</b>	Plevitrexed Phase II trial initiated
<b>1999</b>	Astra and Zeneca merge to form AZ
<b>2002</b>	AZ discontinue development; BTG to take up development
<b>2007</b>	BTG seeking development and commercialisation partner for plevitrexed; Orphan drug designation received

### 6.5.3 Knowledge base (QCA score = 1)

Research contributing to plevitrexed development began in the 1940s with anti-folate research carried out in by Sidney Farber, mentioned in Chapter 2 (Benepal and Judson, 2005). Antifolates were found to be active in their inhibition of thymidylate synthase (TS). Thymidylate synthase was discovered in 1957 and found to be crucial to DNA synthesis. It follows that the inhibition of TS preventing DNA synthesis is associated with abnormal cell growth (Jackman et al., 1985).

In the research stream that followed this discovery there were 317 publications<sup>90</sup> before 1990 (with the first article published in 1961), of which the most frequent author affiliation is Institute of Cancer Research (ICR), UK (affiliated authors of 20 publications over the period up to 1990, Figure 8). The research team at the ICR built on the success of methotrexate and 5-fluorouracil (FU), both antifolate cytotoxic agents, and explored TS as a folate binding site which was a more efficacious target (Jackman and Calvert, 1995). This interest was also supported by Zeneca collaboration (prior to Astra merger in 1999).

The thymidylate synthase inhibitor ICR-AZ collaboration began in the early 1990s. It was around this time that Zeneca and ICR begin to co-author publications in this subject area (Jodrell et al., 1993), and the main related patent was published (Pegg and Wardleworth, 1999a), where earlier patents by the same group covering quinazoline derivatives were

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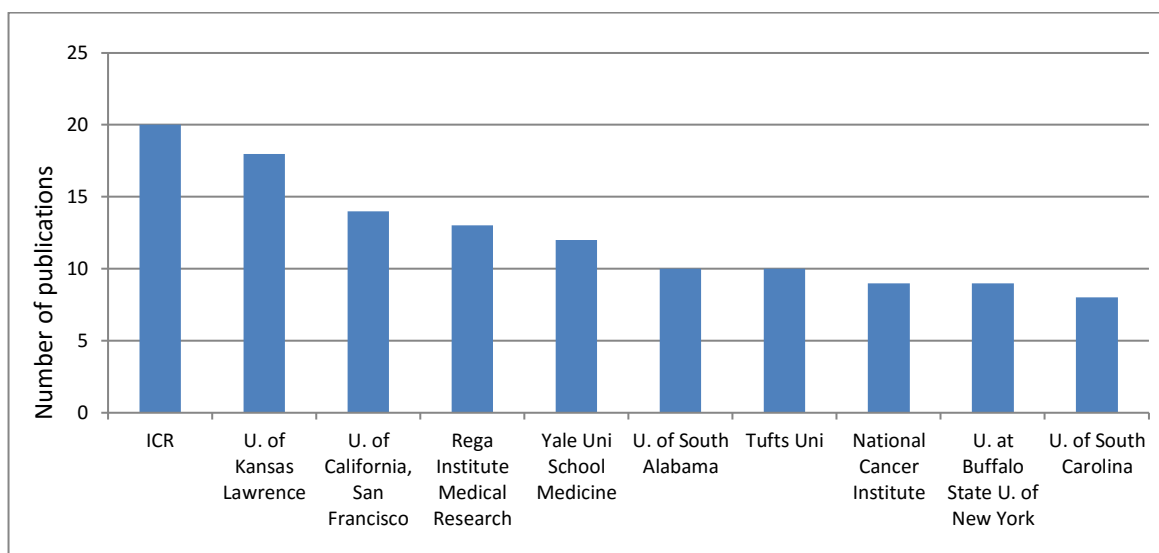
<sup>90</sup> Found in the Scopus database using the search stream (TITLE-ABS-KEY-AUTH ((synthetase OR synthase)) AND TITLE-ABS-KEY(thymidylate) AND TITLE-ABS-KEY(inhibitor))

attributed to the National Research Development Corporation (later to become BTG) (Jackman et al., 1993) and BTG (Bisset et al., 1992).

<u>Generic name</u>	<u>Synonym</u>	<u>Dates under development</u>
CB3717	ICI-155387	1979-1993
Raltitrexed	ICI D1694, Tomudex, ZD1694	Late 1990s/Early 1980s-1996
Plevitrexed	ZD9331	1995-2008

**Table 20 The ICR/AZ anti-folate family of TS inhibitors**

The first clinically evaluated folate-based TS inhibitor arising from the ICR/AZ collaboration, was labelled CB3717 (Jackman and Calvert, 1995). This compound was found to have potent cytotoxicity, partly due to the high levels of polyglutamation<sup>91</sup> it caused in cells (see Table 20). Polyglutamation was also the cause of high levels of toxicity, the eventual reason for discontinuing CB3717 development. However, CB3717 did provide proof of principle for the activity of antifolates on the TS target.



**Figure 8 Top 10 Affiliations of Authors Undertaking TS Research 1961-1989**

The next compound in this series was raltitrexed. Raltitrexed development addressed one of the issues with its predecessor, its lack of solubility. As a report of raltitrexed preclinical work states: 'the identification of ICID1694 [raltitrexed] for clinical study was the result of an extensive search for a second generation, water soluble, folate-based

<sup>91</sup> Simply put, polyglutamation is the process by which glutamates are accumulated in cells, which whilst facilitating cytotoxicity, can also lead to prolonged toxicity when occurring in cells of the bone marrow or bowel lining.

TS inhibitor' (Jackman et al., 1991). These investigations claim raltitrexed to be '500-fold more cytotoxic than CB3717 against a variety of cell lines' (ibid).

Results from raltitrexed phase I trials, investigating 61 solid tumour patients, showed dose limiting toxicities including malaise, gastrointestinal and haematological, as well as other toxicities found in the liver, skin rash and anorexia (Jackman and Calvert, 1995). As a result, a reduced dose of 3mg/m<sup>2</sup> was recommended for phase II. Phase II results showed responses (complete and partial) in breast (25%), platinum resistant ovarian (8.5%), non-small cell lung (10%), pancreatic (14%) and colorectal (26%) cancers, with overall toxicity 'considered acceptable and manageable' (ibid). These results motivated the initiation of a phase III study, undertaken in 1993, comparing raltitrexed administration with FU (fluorouracil)/leucovorin (LV). This indicated that raltitrexed showed higher efficacy, with 20% of patients showing objective partial or complete responses, and lower toxicities, compared to 13% with FU/LV (ibid).

Raltitrexed was approved in 1996 for colorectal cancer, however, the drug was not widely used (Jackman et al., 2008, National Institute for Health and Care Excellence (NICE), 2005, National Institute for Health and Care Excellence (NICE), 2001b).

To improve on the profile of raltitrexed, plevitrexed research was progressed, as an extension to the ICR/AZ collaboration, to identify a product with lower polyglutamation-related toxicities (Jackman and Calvert, 1995). Plevitrexed targeted a different carrier (the reduced-folate membrane carrier) responsible for transporting the folate analogue into the cell (ibid). The aim of this alternative strategy was to increase the selectivity of the antifolate to tumour cells (ibid).

Preclinical development of plevitrexed involved in-vitro testing that identified both curative and growth delay of tumour models, with toxicity only found to be apparent in haematological tissues at the anti-tumour dose studies. Further activity was found in human tumour xenograft models of ovarian, colorectal, gastric and small cell lung cancer.

Early plevitrexed phase I trials, undertaken whilst the project was sponsored by Zeneca/AZ, showed activity in a wide range of tumour types. One phase I study in 14 patients found that associated toxicities included diarrhoea, nausea, vomiting, anaemia, neutropenia, thrombocytopenia, fatigue, fever and skin rash. Another phase I trial tested plevitrexed in combination with carboplatin in 13 patients, 4 patients saw antitumour activity, 2 with dose-limiting toxicity, with no pharmacokinetic interaction found between the drugs. An additional combination study was carried out with cisplatin or gemcitabine.

Around 1997 the project progressed onto phase II trials, in patients of a range of tumour types including gastric, pancreatic, ovarian and advanced colorectal cancers. These trials resulted in 'encouraging activity and manageable toxicity', with particular efficacy found in gastric cancer trials which showed a 25% response rate.

A phase II/III study of plevitrexed comparing it with gemcitabine in 25 pancreatic patients, showed no complete responses, 1 partial response and 10 patients with stabilized disease. However, this trial did indicate that there was a tendency for the drug to prolong life, slow disease progression and lengthen the duration of disease control in patients treated, compared to gemcitabine. In addition, the low patient numbers indicate a lack of statistical validity of the results obtained in this trial. In total 1,094 patients were reported to have been treated with plevitrexed across 22 clinical trials, providing evidence of a substantial opportunity to accumulate relevant knowledge throughout the project's development.

When reporting the decision to terminate plevitrexed development, AZ state that plevitrexed 'failed to meet its target profile' and the rights, along with the preclinical and clinical development data, were returned to BTG, who terminated development after an unsuccessful licensing campaign (AstraZeneca PLC, 2002, Pharmaprojects). This was despite efficacy levels comparable to other competing drugs (Benepal and Judson, 2005).

Up to this point, AZ had carried out over 20 trials in nearly 1000 patients (AstraZeneca PLC, 2002, Pharmaprojects). In addition to the extensive knowledge accumulated throughout plevitrexed development, gastric cancer also shows a high level of accumulated knowledge prior to the initiation of trials (up to and including 1995) of the drug when considering the number of publications (36,160<sup>92</sup>).

This section shows that the development of plevitrexed benefited from being the product of an established research stream in a well-recognised approach to chemotherapy. Furthermore, the knowledge base was further contributed to through the development of the precursor, raltitrexed, whereby the tacit knowledge accumulated, throughout the relatively consistent discovery team (although, as will be evidenced later in this section the teams involved in trials were not as well connected), would have benefited the development of plevitrexed. Taken together these factors justify the QCA score of '1' indicating full membership into the set 'extensive and accumulated knowledge base'.

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<sup>92</sup> This figure was obtained using the Medical Subject Heading (MeSH) term 'Stomach Neoplasms' as a search term in PubMed.

#### **6.5.4 Market demand (QCA score = 0)**

In phase I trials plevitrexed was tested in a variety of tumour types (Aiba et al., 2001, Benson et al., 2003, Benson et al., 2000, Bertucci et al., 1999, Bilenker et al., 2004, Britten et al., 1998a, de Jonge et al., 1999, de Jonge et al., 2002, Goh et al., 2001, Koizumi et al., 2003, Plummer et al., 2003, Plummer et al., 1999, Rees et al., 2003, Schwartz et al., 2004), including leukaemia (Sawyer et al., 2003), gynaecological (Benepal et al., 2005) and ovarian (Benepal et al., 2002) cancers.

In phase II trials there remained an expectation of a broad applicability for the drug. These indications included: non-small cell lung cancer, ovarian and breast (Hainsworth et al., 2003), gastric (Petruzella, 2003), ovarian (Rader et al., 2003), and colorectal (Schulz and Douglass, 2000, Louvet et al., 2004, Schulz et al., 2004) cancer, and one phase II/III in pancreatic cancer (Smith and Gallagher, 2003). Therefore, despite the rarity of the primary indication for plevitrexed, it was apparent that the drug was ultimately applicable to a larger patient population than implied from its first indication.

AZ annual reports confirm the anticipated broad applicability of plevitrexed. In 1999 AZ claim that phase II development of plevitrexed was aimed at solid tumours (AstraZeneca PLC, 1999a). This broad nature of indications for plevitrexed was also found in both the 2000 and 2001 annual reports, when the drug was described as showing efficacy in a broad range of tumours (AstraZeneca PLC, 2000, AstraZeneca PLC, 2001).

When they took over development (upon AZ license termination for strategic reasons, discussed in organisational environment section), BTG planned further development (phase I/II) in gastric cancer (with additional focus on pancreatic cancer) due to encouraging efficacy in advanced gastrointestinal tumours (British Technology Group, 2003b). At this time gastric cancer was described as the second most common cancer worldwide; causing 750,000 deaths worldwide each year (British Technology Group, 2003a). This indicates that BTG focused the development of plevitrexed down to gastric cancer which, despite being a rare disease in the USA and Europe (hence the inclusion in this thesis), could reach a large market potential internationally. In addition, pancreatic cancer is a relatively common cancer, demonstrating that the project was still being developed primarily for cancer indications that represented a large potential patient population. However, plevitrexed was officially recognised as being aimed at a rare disease when US orphan drug designation was granted for ovarian and gastric cancer indications in 2007.

Contrary to the idea that plevitrexed had a large potential market demand, in the years 1999-2000 a number of external analysts predicted low revenues for the drug. These

included Deutsche Bank, predicting sales of US\$12m, and ABN Amro, predicting sales of US\$8m in 2002, rising to US\$66m in 2005 (Niculescu-Duvaz, 2000). In addition, Lehman Brothers, in 1999, predicted a probability of 30% that the drug would reach the market and be launched in 2002 (*ibid*). This evidence demonstrates a small potential market for plevitrexed and low expectations from industry stakeholders, despite the potential for the drug to be applied to additional indications.

The perceived market potential for plevitrexed is likely to have suffered from the disappointment from its precursor product, raltitrexed, which was not recommended by NICE for advanced colorectal cancer (National Institute for Health and Care Excellence (NICE), 2001b, National Institute for Health and Care Excellence (NICE), 2005). Disappointment in the adoption of raltitrexed was also noted by members of the academic science team: 'despite the broad range of activity seen in studies with raltitrexed, it is not widely used, and careful monitoring of renal function with dose adjustments is required to minimize toxicities' (Jackman et al., 2008:207). Furthermore, raltitrexed was not released in the major drug market in the USA due to it not gaining regulatory approval (Wong et al., 2009:174, Business Wire, 1995). This indicates that plevitrexed may have suffered similar difficulties, leading to a diminished perceived potential market demand.

In addition, as observed by one interviewee (email correspondence X), the plevitrexed patents were nearing expiry. The data confirms this, the first patent associated with plevitrexed was filed in 1982, with others following in 1984 (Jones et al., 1986), 1989 (Barker et al., 1992), 1991 (Barker et al., 1993, Andrew et al., 1994), 1992 (Bisset et al., 1995) and 1993 (Pegg and Wardleworth, 1999b, Boyle et al., 1998, Bisset and Bavetsias, 1996) indicating these patents were set to expire around 2013.

Considering the phase II trials began in 1998 and take 2.5 years on average for anti-cancer products, with an additional 4 years for phase III (Abrantes-Metz et al., 2004) accounting for a year in between these, plevitrexed trials would not have been complete until at least 2005 or 2006. In addition, delays from the termination of AZ development and the license reverting to BTG (2002-2007) support the interviewee's observation that a lack of patent protection was a concern. However, this was partially overcome by the designation of the drug under the Orphan Drug Act in 2007, and the extended period of

exclusivity this would have enabled, with the additional potential for supplementary protection certificates<sup>93</sup> upon marketing approval.

This discussion of the market surrounding plevitrexed development indicates it was seen to have broad applicability but these expectations were not widely shared and the drug had disappointing market potential projections. In addition, the compound also suffered from potential patent expiry/appropriability issues impacting the attractiveness of it to prospective licensees. These factors should also be taken into consideration in the context of questioned efficacy data (discussed below).

#### **6.5.5 Stakeholder Perspectives (QCA score = 0)**

Plevitrexed is not commonly cited in the media. In one rare instance financial services firm, Lehman Brothers, predicted a 30% probability that the drug would reach the worldwide markets (Niculescu-Duvaz, 2000), and Morgan Stanley are quoted stating that they believed the project would never reach the market (Dagens Industri, 2002).

One of the only positive perceptions of plevitrexed is expressed in an article highlighting the advantage of the drug being orally administered. In this context plevitrexed is described as potentially the 'first-ever oral anti-metabolite' (Pharma Marketletter, 1997e). However, this article is headlined 'Zeneca Allays Fears Of Near-Term Product Gap' and therefore it is possible that the perception of plevitrexed may have been positively constructed to counter views that the AZ pipeline was dwindling.

After the termination of the AZ license, BTG had sufficiently high expectations of the project to invest in additional trials and apply for orphan drug status. At this time they also compared plevitrexed to other chemotherapeutic agents (both single agents and in combination), claiming higher efficacy than other gastric cancer treatment options (British Technology Group, 2003b). However, this was not sufficient for BTG to continue development without a partner.

The evidence presented here implies a lack of positive perspectives around plevitrexed development. In addition, the characterisation of the project as a cytotoxic agent may have contributed to this negative perception due to the shift towards targeted therapies

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<sup>93</sup> Supplementary protection certificates are available to extent UK patent protection, by five years, for drugs that have successfully received marketing authorisation ([www.gov.uk/guidance/supplementary-protection-certificates](http://www.gov.uk/guidance/supplementary-protection-certificates))

in oncology. These factors contribute towards the designation of the QCA score as '0' indicating non-membership into the set 'positive stakeholder perspective'.

#### **6.5.6 Organisational Environment (QCA score = 0)**

Firm strategy was key to the termination of plevitrexed. As demonstrated in Table 20, plevitrexed was the third thymidylate synthase inhibitor to be developed as a product of an ICR/AZ collaboration. It is both the dynamics of this collaboration and the internal organisational environment of AZ, who took over responsibility for development of the drug after phase II trials, that influenced the development trajectory.

Firstly, early on (in 1994) the collaboration between the ICR and AZ was perceived as 'productive' (Jackman and Judson, 1994). However, there is indication that the relationship may have weakened. In the development of raltitrexed, there was an undercurrent of discontinuity caused by a breakdown of communication between the academic and commercial partner (interviewee J). Whilst toxicities were reported in the publication of results from the raltitrexed phase I trial, there were mechanisms that could be used to overcome these that were not carried forward into the later, larger scale trials (ibid):

"what was highlighted in the Phase I of raltitrexed was that if patients suffered bone marrow toxicity or gut toxicity, which usually took the form of diarrhoea, and [if] you didn't modify the dose then the next time you gave the drug they got very bad toxicity. So the drug only needed to be given once every three weeks because it got trapped in the cells but there was this risk, this threat of cumulative toxicity. And unfortunately, that warning did not really get hammered home, I think, when the drug went into Phase III, so there were a lot of toxicities, some patients died, the drug got a bad name, and the reason that it was not really taken up widely was, I think, because it was deemed to be too toxic. If handled properly, we felt it didn't necessarily have to be toxic." (interviewee J)

Although this may not have had a direct effect on plevitrexed, as it occurred in the development of the precursor, difficulties in communication between academic research institutes and big pharmaceutical firms is observed elsewhere. For instance, pharma are described as 'big destroyers in the navy – they are very powerful but sometimes they are hard to turn around' (interviewee C) or pharma are like an "oil tanker that can't turn" (interviewee L). This observation implies that pharmaceutical companies can be unresponsive to insights of collaborating scientific investigators.

To enquire more into the relationship between big pharma and research institutes, a comparison of nelarabine and plevitrexed was undertaken. Here the cohesion of the



network of researchers is taken as an indicator of the closeness of a collaboration. In this investigation a lack of communication and coordination between the actors was apparent for plevitrexed. In order to show this the authors and organisations for all publications (33 articles) for plevitrexed were compared with those for nelarabine (20 articles).

‘Density’<sup>94</sup> is a measure used in network analysis to indicate the cohesion of a network. The density for plevitrexed is lower than that for nelarabine<sup>95</sup>, in both organisations and individual networks (Table 21). This shows that the cohesiveness of the authors mentioned in the publication of trials for plevitrexed is less than that for nelarabine. In addition, there is no anecdotal evidence for a clear-cut ‘champion’ for plevitrexed, a factor found to be key in nelarabine development.

	Unique Actors (n)	Possible Connections = $n(n-1)/2$	Actual Connections observed	Density
Nelarabine Authors	66	2145	673	0.314
Plevitrexed Authors	115	6555	1028	0.157
Nelarabine Organisations	28	378	260	0.688
Plevitrexed Organisations	37	666	178	0.267

**Table 21 Showing density values for nelarabine and plevitrexed networks, for both authors and organisations**

A critical time in drugs development is in phase II. At this stage the drug is passing from discovery through to development and decision making becomes influenced by other environmental factors, including marketing and finance, which contend with scientific evidence impacting decision making (interviewee J). The shift, from phase I or II on to later clinical development was associated with discontinuities in plevitrexed, wherein

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<sup>94</sup> As discussed in Chapter 3, section 3.1.2, density is the ratio of actual connections between actors, to all possible connections between actors (Balkundi and Harrison, 2006, Scott, 2000). Cohesiveness (i.e. high density) of a network has been found to be related to team performance (Reagans and Zuckerman, 2001, Balkundi and Harrison, 2006). Density is an interesting measure in this context and is appropriate because for both plevitrexed and nelarabine there are a large number of clinical trial publications accessible. For other projects a similar analysis has not been carried out either due to the availability of alternative evidence indicating the consistency of the research group, or the lack of sufficient articles concerning clinical trial results.

<sup>95</sup> Here density was calculated by observing the authors, and organisations listed as being responsible for clinical trial publications for each of the drug projects mentioned. The metric for density is calculated by comparing the number of connections possible with the number of connections observed (actual/possible). The number of possible connections is found using the formula (where N is the number of unique actors)  $N(N-1)/2$ .

management shifted from ICR responsibility towards AZ (interviewee J, also observed from author affiliation in trials publications).

When AZ took on responsibility for plevitrexed development its pipeline, during the late 1990s and 2000s, shows increasing numbers of oncology projects. In 1995 AZ was described as ‘seeking to become the number one company in oncology, which necessitates a move away from its core activities in hormonal therapies’ (Pharma Marketletter, 1995b). This is shown in an increase in the number of oncology projects in development at AZ from 11 in 1999 (AstraZeneca PLC, 1999a) to 25 in 2005 (AstraZeneca PLC, 2005).

However, during this period there is also a shift away from cytotoxic agents (as signalled in Chapter 2), towards more selective, targeted therapies in cancer treatment (AZ pipeline analysis undertaken from annual reports). Publications mentioning other AZ drugs describe this strategy, for instance Wheeler and colleagues (2003): ‘AstraZeneca is developing a broad pipeline of agents targeting a variety of key process in tumour progression and metastasis’. In 2000 AZ describe their oncology strategy as: ‘plans to develop the portfolio [to] include new cytotoxic and endocrine agents and a range of novel approaches’, hinting at an increasing interest in new technologies, whilst maintaining a commitment to cytotoxic approaches (AstraZeneca PLC, 2000).

However, in 2002 their strategy seems to have shifted to emphasise new technologies: ‘development of new agents and novel approaches across a wide range of cancers which include targeting tumour vasculature to control tumour growth, invasion and spread’ (AstraZeneca PLC, 2002). This shift in the AZ oncology portfolio was also felt at ICR:

“I think that [AZ strategy for targeted therapies] may have played a role here. Because at the time that this drug was being developed there was already an assumption, at AZ and in most companies, actually, that the future was targeted therapy. That cytotoxics [like plevitrexed] were old hat, that in 15 years we wouldn’t be using them anymore, that they were yesterday’s drugs and it was wrong to put a lot of investment into them. And you could question whether perhaps the hurdle was set, for success or failure, quite high, because they had already made a decision that they weren’t going to invest heavily into cytotoxics.”  
(interviewee J)

Furthermore, this strategy shift may have manifested in the high threshold set, by AZ, for plevitrexed in terms of the level of efficacy they required to continue development: “it [plevitrexed] never quite got over the hurdle. The hurdle, I have to say... was very high” (interviewee J).

AZ was also a changing organisational environment during this period, commonly associated with the loss of jobs, and disruption in working environments. The major event (Astra merger with Zeneca) occurred in 1999 which coincided with a critical stage in the life cycle of plevitrexed, namely in the year following the initiation of the phase II trials. Indeed the cultural differences between the two companies and associated issues were stated, by the enlarged company's joint executive deputy chairman, Haken Morgen, to be 'the most difficult part of the merger' (Medical Device Daily, 1999). However, AZ were described as being prepared for the challenges, having learnt from the difficulties in the Pharmacia/Upjohn merger four years previously which suffered a "lack of unity of management" (ibid).

When AZ discontinued plevitrexed development the licenses returned to BTG. From the outset BTG announced that, despite initiating phase I/II trial in gastric cancer the company would seek a partner for further development and commercialisation (British Technology Group, 2003b). However, this announcement was followed by another in the same year describing a strategy to undertake in-house development of compounds: a 'strategy to enhance the value of selected pharmaceutical compounds in its portfolio by investing in their preclinical and/or clinical development prior to out-licensing' (British Technology Group, 2004a). This included plevitrexed:

'our aim will be to seek early proof-of-concept before licensing on to a pharmaceutical company partner. This is the model we are using successfully in our other cancer drugs, BGC9331 [plevitrexed] and BGC45' (British Technology Group, 2004b).

This plevitrexed strategy also involved a collaborative partnership with Fulcrum Pharma who were responsible for the clinical development of the project through the phase I/II trial (British Technology Group, 2004a). This phase I/II trial had been fully recruited by March 2006 (British Technology Group, 2006a) and successfully completed later that year (British Technology Group, 2006b). Results showed that of 28 patients that continued to the phase II arm of the trial, 15 showed a stabilized disease.

BTG focused on the possibility that, despite the short patent life, the drug could be useful as an orphan drug for advanced gastric cancer (email correspondence X). With additional clinical results, and the issue of the limited patent life partially resolved with orphan drug status, obtained in 2007, despite initial reports indicating that it was not perceived to be an orphan drug (British Technology Group, 2007), BTG's focus was to make the drug attractive to other firms (email correspondence X). However, results from the trials were not sufficient to bring in external partners and despite an 'extensive

licensing campaign', covering over 100 firms, BTG were unsuccessful and terminated the project (email correspondence X). The action of a key individual, as was the case with nelarabine, may have played a role in facilitating this process whereby personal networks have been shown to be useful in identifying potential partners. This is seen in the development of Campath in the following Chapter.

Indeed, in the 2007 annual report, BTG CEO, Louise Makin is quoted as saying

'Based on the results of this and previous studies we believe that plevitrexed is potentially an important new treatment option for people with advanced or metastatic gastric cancer. We are now seeking a partner to complete the clinical and commercial development of plevitrexed in this and other cancer types'

Similarly, Russell Hagan (Head of R&D at BTG):

'BTG is pleased to have received US orphan drug designation for plevitrexed, our lead oncology compound. We are currently seeking a partner to take plevitrexed further through development and to the market for these important indications as well as potentially in other solid tumours' (British Technology Group, 2007).

In conclusion plevitrexed may have been impacted by the ICR/AZ collaboration that suffered from institutional differences added to through a lack of cohesion in the trial networks. Furthermore, AZ were moving towards a pipeline strategy based on targeted therapy, not applicable to plevitrexed. In addition, the merger between Astra and Zeneca occurred at a critical stage for plevitrexed development. These issues contribute towards project drag whereby the firm's decisions surrounding the drug development progression are increasingly subject to the loss of momentum.

Furthermore, this is not improved upon when the project was taken on by BTG. Here the evidence shows that the firm did not commit to its development and, combined with the lack of patent protection, plevitrexed was not an attractive development opportunity for an external collaborator. These factors can be taken together to contribute to the justification for the QCA score of '0' i.e. non-membership into the set.

#### **6.5.7 Plevitrexed Conclusion**

As this case history has exemplified, the issues associated with the development of plevitrexed were: 1) the established nature and the long duration of the development process, implying patent issues, 2) knowledge transfer issues associated with collaborative agreements between big pharma and academia, and 3) lack of strategic

emphasis due to project being of an established technological pathway, namely cytotoxics agents.

These three issues were inhibitory in the case of plevitrexed, whereby the lack of patent life, combined with the relatively mediocre results from trials, and the lack of strategic interest in technological approach, ultimately contributed towards its termination. These issues culminate in increasing loss of momentum for the project, i.e. project drag, leading to the decision making surrounding the progression of the project to be tainted by lack of enthusiasm.

Furthermore, there may have been a role for the institutional distance between the different types of organisations involved, whereby collaborative partnerships between big pharma and academia research labs require careful management. In addition, complexities in the organisations involved in the trial network and the lack of cohesion seen here may also contribute towards the difficulties in the development of plevitrexed.

## **6.6 Big Pharma Projects – Conclusion**

By analysing projects that were developed involving a big pharma as the main organisation, this Chapter highlighted a baseline project, pazopanib, whereby a relatively uneventful life-cycle with few issues, led to a positive outcome. In contrast we have also exemplified three parallel cases. Firstly, the uncertain nature of knowledge on which novel technological areas are based has been shown to contribute towards the misallocation of expectations, in the case barasertib. The second, nelarabine, underwent a development pathway with many issues but was successfully developed due to the action of a key individual, productive collaborative relationships, and a good organisational culture, in a therapeutic area of unmet need. Finally, plevitrexed, was terminated due to delays, and appropriability risk due to limited patent life, perhaps caused by a lack of efficiency in communication, coordination and integration in project progression, and a lack of strategic fit with the AZ strategy.

Comparatively, pazopanib and barasertib present contrasting scenarios where one underwent unproblematic development (pazopanib) and the other suffered from many issues contributing towards the drugs termination. Nelarabine and plevitrexed are comparable, where both were subject to ongoing collaborative relationships, small market potential, established research pathway and a lack of strategic direction, in terms of targeted therapeutics. However, in contrast to plevitrexed, where there was no clear-cut key individual within the developing firm (AZ), in the case of nelarabine, development benefited not only from influential people promoting development, but also the credibility of previously successful products and the potential to fulfil an area of unmet clinical need.

Of the unsuccessful cases discussed in this Chapter, barasertib and plevitrexed, we observe some interesting characteristics. Firstly, neither seem to be subject to definitive events contributing towards the discontinuation of development. We can conclude that projects based in big pharma are reliant on maintaining momentum, either through rapid development, as was the case in pazopanib, or through the support of key individuals and an established research team, demonstrated in nelarabine. Where project drag occurs contributing towards the loss of momentum, issues are seen to accumulate and therefore development is not prioritised.

In addition, we also observe that despite pharma often citing economic factors as solely contributing towards decisions to terminate development, other contributory factors are additionally causing a loss of motivation to develop the drug. This data indicates that even when there is sufficient efficacy and technological understanding to justify continued support for development, a project may be terminated for an accumulation of reasons.

## 7 Analysis of Rare Cancer Drug Development in Biotech and Academia

This Chapter follows the same format as Chapter 6 but differs in that the analysis follows drug projects that were originated by, or in collaboration with, a small biotech or academic research lab. This will form the basis for the descriptive analysis to follow, and provide justification for the QCA scores allocated.

Prior to the case histories it is first relevant to compare the organisations involved in individual projects. Figure 9 and Figure 10 show a diagrammatic representation of the dynamics of the organisations involved in drug discovery and development, and the phases of their involvement. The dotted lines represent phases characterised by organisational shifts, for instance, in the case of nelarabine, where Wellcome and Glaxo merge, and again when Glaxo Wellcome and SmithKline Beecham merge. In this instance the continued involvement of Duke University is represented as separate arrows to indicate that the collaboration continued despite the changes to the main firms. In contrast, where SUGEN enters in only in discovery phases the right hand side of the dotted line in the case of barasertib is where AZ were solely responsible.

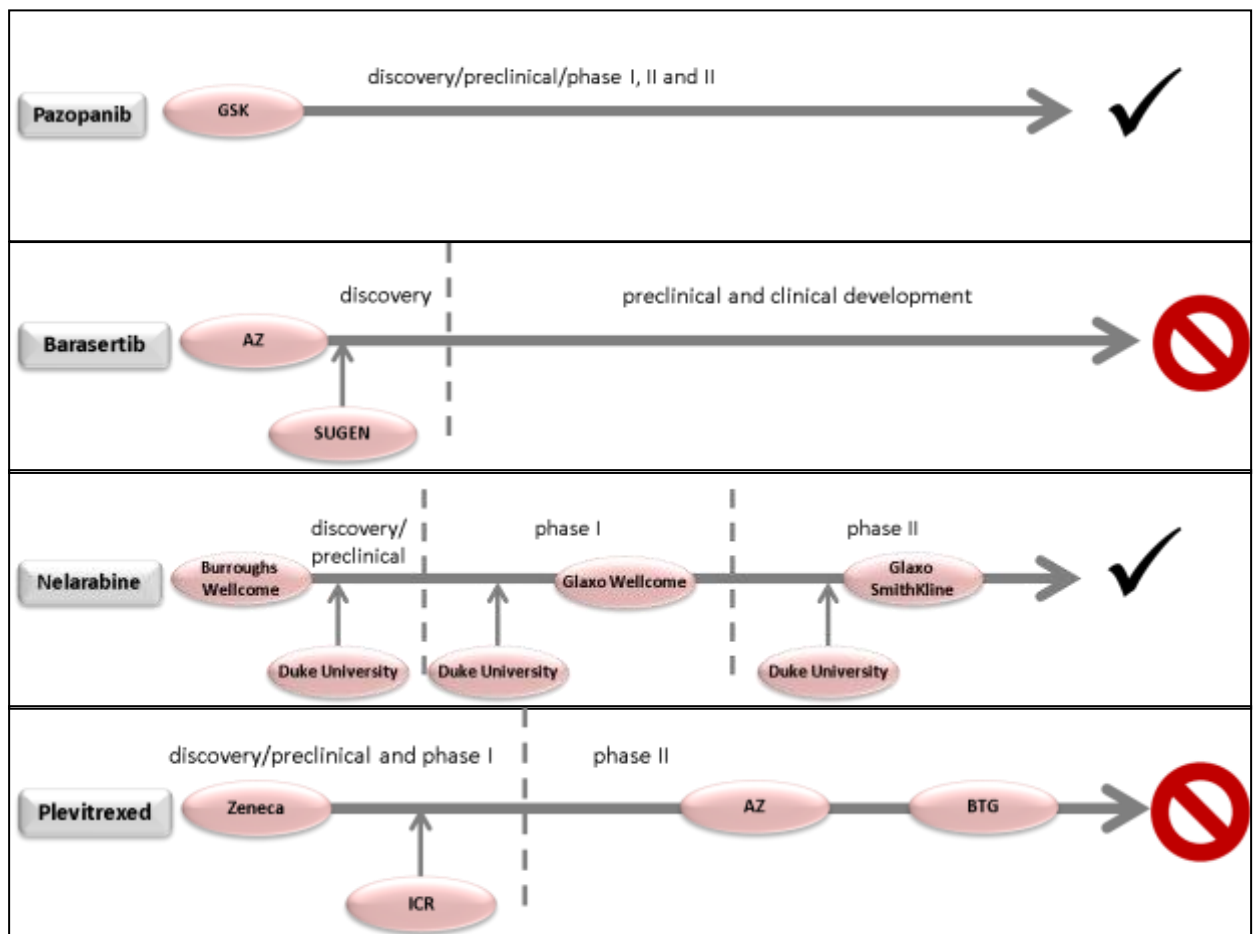


Figure 9 Organisational dynamics in drug projects involving big pharma

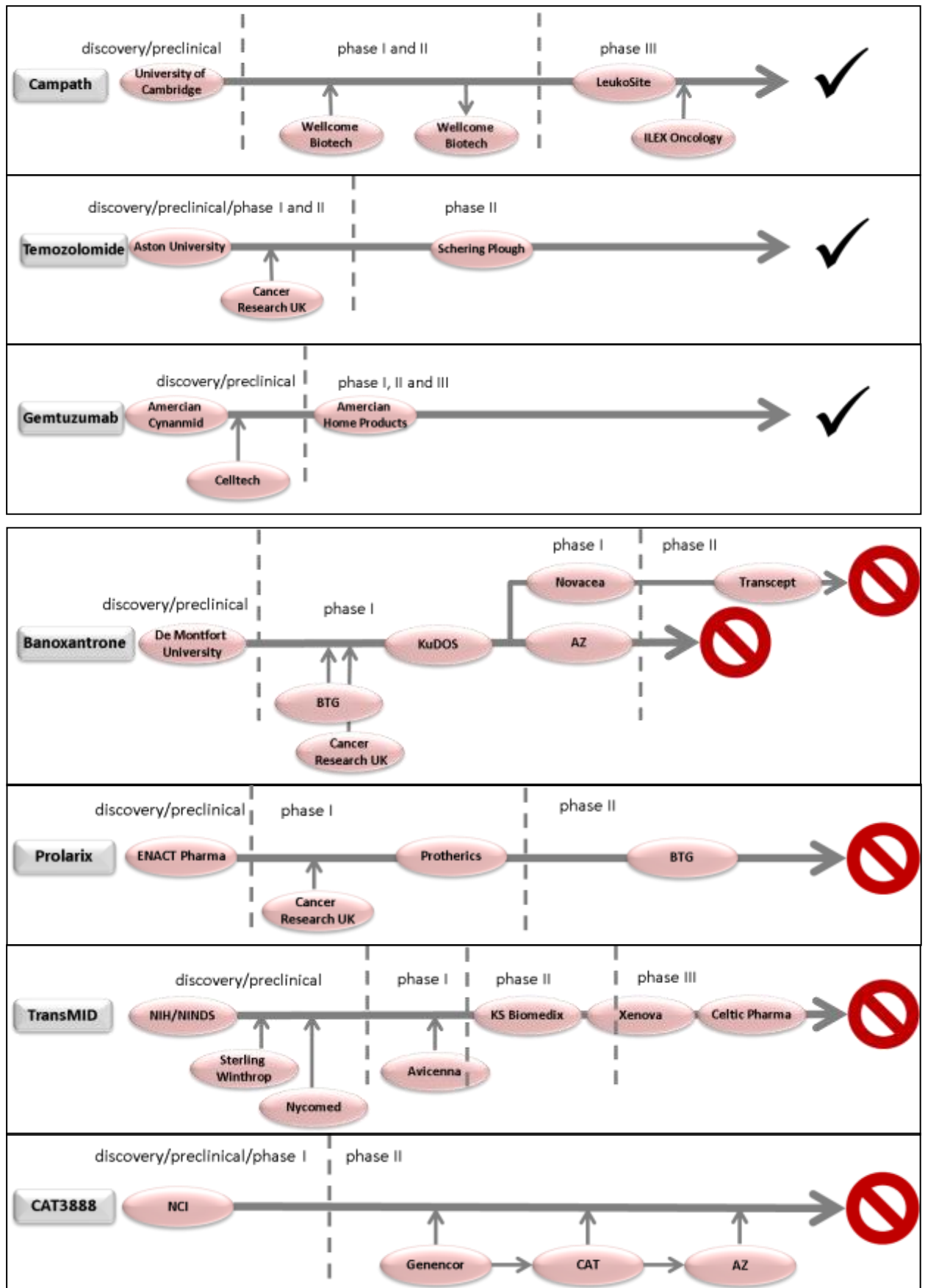


Figure 10 Organisational dynamics of projects involving academia and biotech



Unsurprisingly the drugs with involvement from big pharma had relatively simple trajectories in terms of the organisational involved in development (see Figure 9). In contrast, projects that had major involvement from small biotech firms, or academia, were, in general, subject to a larger number of collaborative and licensing agreements and associated changes in their organisational context. In fact, of the projects that either had substantial involvement from academic or research institute scientists, or were located in biotech firms, the majority (5/7) went through a complex chain of different organisational structures and transactions. In particular, Campath, banoxantrone, Prolarix, TransMID and CAT3888 show a complex network of organisations involved in development (compared to temozolomide, gemtuzumab and CAT3888) (Figure 10).

Chapters 2 and 3 explored literature demonstrating the more networked nature of the industry and the reliance of innovation on external sources of innovation. The extent to which this is observed on a project level, and the issues this causes, is not well understood. We can assume that these issues are associated with the transferral and integration of tacit knowledge accumulated throughout development. This thesis provides a foundation for furthering this understanding by exploring the paths projects take involving different organisations.

As well as continuing to relate the case histories to the concept of project drag this Chapter also draws on 'protected spaces' as a way to understand the influence a small firm environment has on drug development. As mentioned in Chapter 3, protected spaces are created when individual expectations are mobilised and become shared, collective expectations. These create a protected space by which stakeholders surrounding the technology suspend evaluations and selection pressure no longer act. We apply this notion to a firm level, by which small firms undergo a process of vision shared which leads to the perception that issues are conquerable.

We propose that in this environment where issues would be expected to contribute towards project drag, this process is not consciously recognised until the protected space is broken and the issues are unveiled. We see this to be the case in TransMID, banoxantrone and CAT3888, whereby merger and acquisition (M&A) events led to a rapid termination of the project, taken to be a sign of the breakdown of protected space and the implementation of objective evaluation processes by the acquiring firm.

## **7.1 Temozolomide – Charity Support**

Temozolomide (CCRG-81045, M&B-39831, NSC-362856, RP46161, Sch52365, temodal, temodar, temoxol) was successfully approved for glioblastoma. The project was marred by: 1) limited market potential, and 2) a problematic (established and

unstrategic<sup>96</sup>) technological pathway, however, these issues were resolved due to the early support and involvement of a prominent cancer charity, Cancer Research UK, and the action of a key individual. If we assume that, particularly in the UK, due to limited resources, all projects stemming from academic or small firm R&D require a pharma partner later on in development, temozolomide provides an ideal type for projects originating in small biotech and/or academia. This is due to the charity support providing sufficient funding and development to ready the project for pharma licensing. An alternative ideal type is found in gemtuzumab, in which drug discovery and development resulted from a collaborative effort involving academia at very early stages, followed by biotech and pharma.

While temozolomide is an ideal type (for charity/academia/pharma development) it also presents an unusual development trajectory. In general, partnering between academia and industry occurs via a biotech intermediary bridging discovery with later stage development. As observed in the biomedical innovation literature, this pattern stems from the institutional and cultural differences inhibiting academia and big pharma relationships. In addition, academic and biotech labs lack the necessary financial resources to prepare the project for pharma in-licensing. Furthermore, pharma struggle to form and maintain relationships with the multitude of academic centres so biotech have a role in incubating potential projects, feeding into pharma at later stages.

In contrast, to this common trend (of academic projects passing to pharma via a biotech intermediary) temozolomide was financially supported throughout early stage development providing sufficient evidence for Schering Plough (SP) to in-license. This is important as highlighted by one key individual who suggests the project may not have succeeded in a less supportive organisational environment (Stevens, 2008).

### **7.1.1 Interview sources**

No interviews were undertaken to inform this case history, however, an email correspondence was used to clarify and add additional points (referred to as email correspondence V).

### **7.1.2 Introduction**

Temozolomide is a DNA alkylating agent imidazotetrazine derivative, developed by an academic research group at Aston University, supported by Cancer Research (CRC)

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<sup>96</sup> Here, we assume that the development of a cytotoxic would be unstrategic due to the general direction of the industry towards targeted therapeutics for cancer drugs.

and SP. Temozolomide received accelerated approval in 1999 (FDA and EMA) for the treatment of glioblastoma multiforme and anaplastic astrocytoma (rare forms of brain tumour).

<b>1980</b>	Synthesis of mitozolomide and temozolomide
<b>1984</b>	Mitozolomide Phase I trials done in early 1980s (funded by CRC (CR-UK and May & Baker)
<b>1992</b>	Phase II trials in temozolomide initiated, funded by CRC; licensing agreement with Schering Plough
<b>1993</b>	US Patent granted
<b>1996</b>	Carmustine implant (competitor for glioblastoma market) approved as adjuvant to surgery in glioma patients
<b>1998</b>	Orphan Drug status granted to temozolomide
<b>1999</b>	Temozolomide approved
<b>2001</b>	NICE approval for recurrent malignant glioma patients who have failed 1 <sup>st</sup> line treatment

**Table 22 Key events in development of temozolomide**

### **7.1.3 Knowledge base (QCA score = 1)**

The chemistry that contributed towards the development of the imidazotetrazines began in the 1880s, when the chemical precursor to mitozolomide (the first compound in the temozolomide family) was synthesised. This involved knowledge of triazenes and triazines, which led to the discovery of the anti-tumour imidazotetrazines (Stevens, 2008:158).

Biochemical pharmacology work, undertaken by Tom Connors (CRC) and colleagues, revealed that the adaptation, through demethylation (removal of the methyl group), of these compounds could induce an antitumour effect (ibid). In addition, research conducted by Malcolm Stevens and colleagues in the 1970s, initially at Nottingham University and then at Aston University, began focusing on the synthesis of nitrogen-rich heterocyclic systems and later, their chemical and biological properties (ibid).

In 1978 the pharmaceutical company May & Baker sponsored a pharmacy postgraduate, Robert Stone, to work with Stevens' team investigating the anti-allergy properties of bicyclic compounds (Stevens, 2008:159). However, these compounds were abandoned in favour of research leading to the preparation of the first bicyclic system compound, from the combination of an imidazole ring and a tetrazine ring (ibid). The resulting product was mitozolomide (Stevens et al., 1984). Due to the multidisciplinary nature of the research team it was possible for antitumour activity in mouse models, to be ascertained (Stevens et al., 1984, Stevens, 2008, Hickman et al., 1985).

Mitozolomide phase I trials began in 1983 when the project was fast-tracked into the clinic at Charing Cross Hospital by Edward Newlands and George Blackledge sponsored by May and Baker (Stevens, 2008, Sansom, 2009). Mitozolomide, which was found more active than temozolomide in mouse models (email correspondence V), also showed high bone marrow toxicity in phase I trials (Newlands et al., 1985, Stevens, 2008, Sansom, 2009). This toxicity was identified to have stemmed from the DNA-cross linking properties of the molecule, requiring a structural change which was achieved in the production temozolomide (Stevens, 2008).

Temozolomide underwent preclinical testing at Aston University (now under the sponsorship of the CRC after May and Baker discontinued interest in the project) where it was screened against murine tumours in vivo, in cells lines ranging from leukaemias to sarcoma and melanoma (Stevens et al., 1987). The promising antitumour activity observed from this testing led to the CRC's Phase I/II trial Committee agreeing to fund a temozolomide clinical trial (Stevens, 2008). This phase I was undertaken in a total of 51 patients, indicating some toxicity, used to inform the maximum tolerated dose, but not at the level of severity seen for mitozolomide (Newlands et al., 1992). Additional phase I trials were also carried out by the CRC (Brock et al., 1998, Smith et al., 1990).

Positive results from these phase I trials led the CRC to sponsor, unusually given the high costs, further phase II trials in glioma (Bower et al., 1997), non-Hodgkin's lymphoma (NHL) (Woll et al., 1995) and melanoma (Bleehen et al., 1995). The glioma trial results showed 11% of patients achieving an objective response, and a further 47% with stable disease, with some predicted toxicity (Bower et al., 1997). In NHL 18 patients were treated, with only one partial response contributing to the conclusion that this indication was not suitable for treatment with temozolomide (Woll et al., 1995). In metastatic melanoma 60 patients were treated with 3 showing a complete response, and 9 a partial response (Bleehen et al., 1995).

As a result of these findings SP licensed temozolomide, however, as the CRC trials were not conducted in line with Good Clinical Practice (GCP) guidelines, SP undertook additional phase I and II trials (Brada et al., 1999, Baker et al., 1999, Britten et al., 1998b, Britten et al., 1999, Dhodapkar et al., 1997, Estlin et al., 1998, Hammond et al., 1998, Hammond et al., 1999, Moore et al., 1998, Nicholson et al., 1998, Yung et al., 1999).

In 1998 results of a phase II/III registration study in 225 patients with glioblastoma multiforme were presented at the European Association for Neuro-Oncology Meeting (Schering Plough, 1998). This trial showed progression-free survival at 6 months to be higher in the temozolomide group than the control (ibid). In addition, temozolomide

treated patients had better overall survival than the control group (ibid). These results led to the approval of temozolomide in Europe and the USA in 1999.

**Table 23 Showing publication frequency of key individuals involved in temozolomide trials**

Authors	Number of articles (total of 20)	Papers
Newlands	7	(Newlands et al., 1992, Oreilly et al., 1993, Bleeheh et al., 1995, Woll et al., 1995, Newlands et al., 1996, Bower et al., 1997, Brock et al., 1998)
Brampton	7	(Newlands et al., 1992, Oreilly et al., 1993, Bleeheh et al., 1995, Woll et al., 1995, Newlands et al., 1996, Bower et al., 1997, Brock et al., 1998)
Statkevich	6	(Estlin et al., 1998, Britten et al., 1998b, Brada et al., 1999, Hammond et al., 1999, Britten et al., 1999, Baker et al., 1999)
Dugan	6	(Estlin et al., 1998, Britten et al., 1998b, Brada et al., 1999, Hammond et al., 1999, Baker et al., 1999, Yung et al., 1999)
Rowinsky	5	(Britten et al., 1998b, Hammond et al., 1998, Hammond et al., 1999, Britten et al., 1999, Baker et al., 1999)
Reidenberg	5	(Estlin et al., 1998, Britten et al., 1998b, Brada et al., 1999, Hammond et al., 1999, Baker et al., 1999)
Von Hoff	4	(Britten et al., 1998b, Hammond et al., 1998, Hammond et al., 1999, Britten et al., 1999)
Stevens	4	(Newlands et al., 1992, Oreilly et al., 1993, Bleeheh et al., 1995, Estlin et al., 1998)
Colquhoun	4	(Oreilly et al., 1993, Newlands et al., 1996, Bower et al., 1997, Brock et al., 1998)
Baker	4	(Britten et al., 1998b, Hammond et al., 1999, Britten et al., 1999, Baker et al., 1999)
Eckardt	4	(Britten et al., 1998b, Hammond et al., 1998, Hammond et al., 1999, Britten et al., 1999)

During the development of temozolomide there was consistency in the investigators involved in trials indicated through the high level of co-authoring in trial publications, shown in Table 23.

In the knowledge accumulated around the primary indication, temozolomide benefitted from 18,504<sup>97</sup> published glioma articles (up to and including 1992), indicating a large disease-associated scientific literature.

The evidence presented here indicates that the development of temozolomide was based on an established area of research, and benefited from learning from a precursor molecule in mitozolomide. This demonstrates a justification for the allocation of the QCA

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<sup>97</sup> This figure was obtained using the Medical Subject Heading (MeSH) term 'Glioma' as a search term in PubMed.

score of '1' representing membership into the set 'extensive and accumulated knowledge base'.

#### 7.1.4 Market demand (QCA score = 1)

Early preclinical and trials for temozolomide, carried out by the CRC focused on general solid tumours illustrating a broad applicability for the drug (Brock et al., 1998, Newlands et al., 1992, Smith et al., 1990, Stevens et al., 1987). Phase II trials were undertaken in a range of tumours, despite the glioblastoma primary indication. Undertaken by CRC, trials were undertaken in glioblastoma multiforme (Bower et al., 1997), melanoma (Bleehen et al., 1995) and non-Hodgkin's lymphoma (Woll et al., 1995). In addition, on the SP license phase I studies were undertaken in a range of tumour types (Brada et al., 1999, Britten et al., 1999, Hammond et al., 1998, Hammond et al., 1999, Britten et al., 1998b, Baker et al., 1999, Estlin et al., 1998, Nicholson et al., 1998), and with phase II trials expanding the range of indications, including astrocytoma (Yung et al., 1999), pancreatic (Moore et al., 1998) and nasopharyngeal (Chan et al., 1998) cancers. This represents a large potential market demand for the temozolomide drug project (see Table 24).

Indication	Incidence per 100,000 in USA	Deaths per 100,000 in USA	Year
Brain and other nervous system (including glioblastoma and astrocytoma)	6.4	4.3	2007-2011
Melanoma	21.3	2.7	2007-2011
Non-Hodgkin's Lymphoma	19.7	6.3	2007-2011
Pancreatic	12.3	10.9	2007-2011
Nasopharyngeal	1	No data	No data

**Table 24 Incidence and mortality rates for indications relevant to the development of temozolomide (i.e. indications for which the drug was tested in trials) (source: SEER data)**

There was no quantification of the expected market demand for temozolomide during the drug's development. However, in addition to the potential for temozolomide to be applied to a broad range of indications following initial approval, it was also likely that temozolomide could demand high prices due to the unmet need in glioblastoma<sup>98</sup>.

When temozolomide was developed brain tumour patient treatment options were limited, despite the approval of the carmustine implant in 1996. The carmustine implant involves

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<sup>98</sup> Indeed when temozolomide was approved it did demand high prices, whereby one cycle of treatment cost between £934 and £1,176 in 2001 (NICE, 2001)

the insertion of a wafer into the brain administering carmustine (an approved cytotoxin) to the tumour site as it dissolves<sup>99</sup>. This procedure is invasive, particularly when compared to the oral administration of temozolomide. Considering the ability for temozolomide to fulfil an unmet need, in addition to orphan drug status being granted to the drug in 1998, issues associated with the low market potential of the primary indication were overcome.

Patents for temozolomide were granted in 1991 (Lunt et al., 1993) and 1993 (Stevens et al., 1997). Therefore, despite the long development duration, the loss of patent protection was not an inhibitory issue to the development of the project, as they were not set to expire until 12 years subsequent to drug approval.

For temozolomide the QCA score of '1' for membership into the set high market demand is justified through the range of tumour types explored in trials, indicating a high potential market. This is further supported by the lack of competition and unmet clinical need in the brain tumour indication.

#### **7.1.5 Stakeholder Perspectives (QCA score = 1)**

Stakeholder perspectives of the development of temozolomide were represented by academic investigators, CRC, SP and, perhaps most interestingly, patients who came across the drug during clinical development.

Firstly, the academic investigators responsible for discovery and early stage development of the drug had high expectations of the drug. For instance, the group has been reported to have thought that they had found 'the elusive "magic bullet" against cancer' (Sansom, 2009). However, the disappointing results in early temozolomide trials were described as 'disastrous' (Stevens, 2008).

High expectations were shared by the CRC who funded the early stage work and supported temozolomide in trials. This first trial of temozolomide was relatively early on in the history of the CRC Phase I/II Trials Committee (which was founded in the early 1980s), and motivated additional larger trials to be initiated by CRC (Newell et al., 2003, Arney, 2013). These would have involved substantial investment from CRC implying a promising perception of the project.

The involvement of a high profile cancer charity, and the publicity this enabled, contributed towards a positive public perception of the drug. For instance, temozolomide

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<sup>99</sup> [www.cancer.gov/about-cancer/treatment/drugs/carmustineimplant](http://www.cancer.gov/about-cancer/treatment/drugs/carmustineimplant)

was described as a 'shining example of how the public's generous support of CR-UK has directly benefited the lives of people with cancer' (Arney, 2013). In addition, the agreement with SP was a ground breaking moment in the history of charity-supported drug development in the UK, described as 'the first marketing deal of its type by a British charity' (Farmer, 1992).

In addition, when SP licensed temozolomide, the company had high expectations of the project, considering both its history of encouraging results (50% response rates in patients) and the drug's ability to fulfil an unmet need:

'temozolomide offers the possibility of giving the worldwide medical community an important new anticancer agent for the treatment of gliomas, a devastating disease poorly treated by current therapies' (Schering-Plough Corporation and Cancer Research Campaign Technology Limited, 1992).

In line with these high expectations from SP, there was also high demand for temozolomide from patients and physicians, with the compassionate use programme approved in October 1992, which was publicised widely. For instance, The Guardian and The Daily Mail (The Guardian, 1992, Hope, 1992) reported the offer of temozolomide on a compassionate use basis at CRC units across the UK. This implies that patients and physicians supported temozolomide due to the potential that the drug could fulfil an unmet clinical need.

Patients' high expectations of temozolomide are further illustrated in media reports of fundraising by patients. For instance, in November 1992 the drug was mentioned in the Daily Mail, reporting fundraising by an aircraft commander, who was hoping to access £50,000 for CRC to increase production of the drug (Daily Mail, 1992). Additional articles in the media report patient experiences, for instance:

'One of the first to try the drug [temozolomide] was mother-of-two Theresa Bouette, 40, of Winchmore Hill, North London. Despite two operations, she said, she was 'unsteady on my feet, my speech was slurred and I had severe memory loss'; the drug had 'transformed my life.'" (O'Shea, 1992)

From 1993 to 1997 temozolomide did not appear in media reports with the exception of a report of a young woman with a brain tumour, published in the Washington Post in March 1997 (Colburn, 1997). The woman was taking temozolomide on compassionate grounds, when the drug was between phase I and phase II. The report of the drug was positive, with only limited side effects and the patient leading a relatively normal life whilst trying to fight her brain tumour (ibid).



This evidence indicates that temozolomide was developed surrounded by a range of positive stakeholder perspectives. This ranges from academics who term the drug a 'magic bullet' to the CRC support of trials. Furthermore, compassionate use and patient stories indicate that users, patients and physicians were also enthusiastic. These stakeholder perspectives are generally positive justifying the QCA score of '1'.

#### **7.1.6 Organisational environment (QCA score = 1)**

Temozolomide was supported by public/charitable funding, with an industrial partner present at the very early stages of the development of the precursor molecule, and again only after the drug had been extensively studied in phase I and II trials.

As mentioned discovery work contributing to temozolomide was undertaken at Aston University. At this time the synthesis, testing and preclinical research was funded by a combination of May and Baker, Aston University and the Science and Engineering Research Council (through studentships) (Stevens et al., 1984, Hickman et al., 1985, Stevens et al., 1987). In 1978, Stevens told Stone, the May and Baker post-doctoral researcher, to 'make some interesting molecules' to test for antitumour activity (Sansom, 2009). This indicates that temozolomide resulted from the trial and error approach to cancer therapeutics, as opposed to rational drug design.

May and Baker funded the phase I trial in mitozolomide but discontinued support when phase I trials showed inhibitory toxic effects (Stevens, 2008, Sansom, 2009). When May and Baker discontinued support the CRC Phase I/II Trials Committee (the forerunner to the current Drug Development Office) decided to finance further trials, which were undertaken at the Charing Cross Hospital, Mount Vernon Centre for Cancer Treatment, the Queen Elizabeth Hospital and the Aston University (Newlands et al., 1996, Brock et al., 1998, Oreilly et al., 1993, Newlands et al., 1992, Smith et al., 1990).

In 1984 there were issues with temozolomide manufacturing. This was due to its reliance on methyl isocyanate, which was involved in an incident in India (Bhopal), described as a 'catastrophic toxicological disaster' causing long lasting effects in a densely populated area (Stevens, 2008). This motivated the development of a new way of synthesising the compound for early stage trials (ibid).

In the early 1990s, prior to the publication of phase I and II results, Stevens led a team of these investigators on a 'roadshow' around the US 'presenting the early clinical data to potential partners' (Sansom, 2009). This resulted in the SP licensing agreement.

At the time of the SP license oncology therapeutics were one of the firm's top priorities. This is demonstrated in a press release in late 1991, where there are five therapeutic

areas identified as being key in the SP strategy, including anti-cancers (PR Newswire, 1991). Furthermore, as a big pharma with an established over-the-counter, and therapeutics business, SP had the resources and experience to develop temozolomide.

The organisational environment surrounding temozolomide development indicates that there was a consistent research team and despite this changing when SP licensed the drug there is no data indicating how smoothly this transition occurred. However, the phase I and phase II proof of concept trials had already been completed, sponsored by the CRC. In addition, the replication of trials by SP indicates that the new research team accumulated their own observations and knowledge around temozolomide, lessening the need for the transfer of accumulated knowledge. This justifies the QCA score (1) indicating a supportive organisational environment was present in the development of temozolomide.

#### **7.1.7 Temozolomide Conclusion**

Temozolomide is described, by the discovering scientist, Malcolm Stevens, as an illustrative case of project supported by a diverse group of collaborators, both in disciplines and institutional backgrounds (Stevens, 2008). Despite this diversity, the progression of the project was also reliant on a key individual operating across the frontiers of these disciplines, and providing leadership. In this case Malcolm Stevens provided this role and was able to do this as a result of support from money from CR-UK. This support provided sufficiently strong evidence to interest the SP license.

In addition, temozolomide benefited from the presence and support of CRC, throughout the lab research and early stage trials. As Stevens observes, on several occasions the project 'teetered on the brink of extinction', and 'had the project been exclusively the possession of industry, doubtless it would have fallen at the first hurdle' (Stevens, 2008).

### **7.2 Campath – Key Individuals Rescue a Path-Breaking Drug**

The development of Campath (alemtuzumab) began in an academic research team, in collaboration with a small biotech subsidiary of a big pharma. When the partner, Wellcome Biotech, discontinued the license a US biotech in-licensed and took the drug through to approval.

During development the issues facing the project were: 1) novel and uncertain nature of the markets, 3) novel and uncertain nature of the knowledge, 4) potential difficulties associated with transferring knowledge between different firms and 5) potential vulnerabilities to the small firms involved at later stages of development, i.e. to industrial dynamics, and lack of experience, competencies and capabilities. These issues

contributed towards project drag which motivated the license termination by Wellcome. However, the effects of this project drag, were not fatal for Campath and were overcome by the action of key individuals, and the high expectations and excitement over the use of a novel therapeutic modality.

Additional mechanisms acting to aid in the success of Campath were the range of potential indications it could be applied to, the granting of orphan drug status, the knowledge accumulated throughout development, the excitement for the new technological approach applied and the role of both key individuals and patient user groups.

### 7.2.1 Interview sources

Interviews were carried out with individuals involved in the drug discovery and development process. This included interviewee A, interviewee B and interviewee C.

### 7.2.2 Introduction

Campath is a mab targeting the CD52 antigen approved for the treatment of chronic lymphocytic leukaemia (CLL) patients, in 2001 (FDA). The project originated in the pathology laboratory at the University of Cambridge, with an initial license taken out by Wellcome Biotech in 1985. However, when this was discontinued in 1994 LeukoSite took on development to approval.

<b>1985</b>	Wellcome licenses rights to commercially develop Campath
<b>1986</b>	Winter's humanisation method developed
<b>1988</b>	Campath first tested in humans; Therapeutic Antibody Centre (TAC) opens; Campath-1H developed
<b>1992</b>	Campath in Phase I for Rheumatoid Arthritis (RA) and Phase I/II for NHL
<b>1993</b>	Campath in Phase II for CLL
<b>1994</b>	Wellcome discontinues license due to disappointing results in trials for RA and NHL
<b>1995</b>	TAC moves to Oxford with funding from MRC and LeukoSite
<b>1997</b>	LeukoSite take on development of Campath, in collaboration with ILEX Oncology; orphan drug designed by FDA
<b>1998</b>	Pivotal Phase III trial in CLL begins
<b>2001</b>	Campath approved by the FDA

**Table 25 Key events in development of Campath**

Campath went through several incremental changes in development. The first molecule, Campath-1M, used a murine mab to target CD52. The second, Campath-1G, involved

adaptations to the antibody to improve response rates in patients. The final change to Campath was in the humanisation of the antibody, to produce Campath-1H. In this case history we will refer generically to 'Campath' due to the focus of the drug on CD52 and the same metabolic pathway.

### 7.2.3 Knowledge base (QCA score = 1)

Campath is 'one of the oldest therapeutic mab ever created' (Marks, 2013a), and one of the first to be prioritised for commercialisation by a private company (Hale and Waldmann, 2000, Clark, 2005, Marks, 2015).

After joining the Department of Pathology (University of Cambridge), Waldmann was introduced to the production and use of mabs in 1974, when he encountered Georges Kohler. Waldmann's interest in mabs stemmed from his attendance at a presentation by Milstein and Kohler prior to their 1975 hybridoma publication (Marks, 2013a, Marks, 2015). In 1978 Waldmann took a sabbatical at Cesar Milstein's<sup>100</sup> Laboratory (Clark, 2005).

Waldmann explored the potential for mabs to be used as tools in investigating immune tolerance. However, Campath was found to have the ability to kill lymphocytes, leading to a realisation that the drug could be applied to GvHD in bone marrow transplants (*ibid*). Waldmann and Hale state: '[it was] clear that certain anti-T cell mabs, of appropriate isotype could be exploited as agent to kill lymphocytes *in vivo*' (Waldmann and Hale, 2005).

At this time Waldmann 'discussed plans to apply for an MRC programme grant to make mabs for the purpose of removing T-cells from human bone marrow to treat the problem of Graft vs. Host Disease (GvHD)<sup>101</sup> (Clark, 2005, Hale and Waldmann, 2000). This was successful in 1980, and the MRC programme grant (Clark, 2005, Marks, 2013a, Marks, 2015) is mentioned in acknowledgements in research papers up to 1999. The MRC grant facilitated expansion of the research team, in 1981, and the recruitment of multidisciplinary scientists (Clark, 2005, Marks, 2013a, Marks, 2015). Sooner after a family of antibodies were found providing the precursor of Campath (Hale and Waldmann, 2000, Clark, 2005, Marks, 2013a, Marks, 2015). At this stage it was not clear which

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<sup>100</sup> Milstein later received The Nobel Prize in Physiology or Medicine for his work on MABs.

<sup>101</sup> GvHD was known to be caused, in bone marrow transplants, by the new transplanted tissue (graft) attaching the recipient (host) tissues. By the time of Waldmann's investigations, it was appreciated that GvHD was caused by the 'contamination of the bone marrow from mature t-lymphocyte cells' (Marks, 2013a, Marks, *forthcoming*)

antigen was targeted by the antibody, however, after characterisation by Geoff Hale it was realised that the antibodies targeted the CD52 antigen (Hale and Waldmann, 2000)

This sequence of events, in the discovery of the antibody preceding the antigen is further illustrated in publication metrics wherein articles mentioning CD52<sup>102</sup> prior to Campath phase I initiation (1992) amount to just 15. However, when the PubMed search is undertaken including Campath<sup>103</sup> as a search term the number increases to 103.

When a suitable antibody was selected and initial laboratory testing completed, preclinical studies of Campath-1M were carried out. The results led to the initiation of the first human pilot study (Marks, 2013a, Marks, 2015). In 1982 the first patient, a man suffering from NHL, was treated with Campath-1M (Hale and Waldmann, 2000, Marks, 2013a). Despite the treatment showing some activity, the effects were only temporary and the patient died soon after (Marks, 2013a, Marks, 2015). However, no toxicities were observed and the patient tolerated the treatment well. The temporary effects of Campath were also seen in other mabs at the time (Marks, 2013a, Marks, 2015). Additional pilot studies were carried out in patients with leukaemia and aplastic anaemia, showing effectiveness, tolerance and little toxicity (Marks, 2013a).

The temporary effects found in trials were suggested to be due to the IgM antibody present in Campath-1M which, produced by the body's immune system in response to a foreign body, exists only temporarily. Waldmann's team began exploring ways of adapting Campath to combat this as it was anticipated that changing the antibody to the IgG antibody which would produce long-term immunity and a persistent response in patients (Marks, 2013a, Marks, 2015). However, this was challenging and involved the study of the structure of mabs and the screening of 20 million clones (Marks, 2013a, Marks, 2015). The resultant mab was discovered in 1985 and dubbed Campath-1G.

The first patient to be tested with Campath-1G had CLL, and was treated in 1987 (Marks, 2013a, Marks, 2015). The response in this patient exceeded Waldmann and Hale's 'most optimistic expectations' (Hale and Waldmann, 2000, Marks, 2013a, Marks, 2015). Nonetheless the patient later died due to underlying disease.

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<sup>102</sup> Search term used: (cd52[All Fields] OR cdw52[All Fields]) AND ("1900/01/01"[PDAT] : "1992/31/12"[PDAT])

<sup>103</sup> Search term used: ((cd52 OR cdw52 OR Campath)) AND ("1900/01/01"[Date - Publication] : "1992/31/12"[Date - Publication])

Soon after the initiation of CAMPATH-1G trials, Gregory Winter developed a method for producing humanised mabs (in 1986) and collaborated with Waldmann to produce a humanised form of Campath ((Hale and Waldmann, 2000, Marks, 2013a, Marks, 2013b). The aim of this method was to decrease the levels of the foreign component (in this case murine) of the mab while increasing the human component (Marks, 2013a, Marks, 2015). This was thought to influence the tolerability of the molecules in the body, by decreasing the immune responses against them (Marks, 2013a, Marks, 2015).

The agreement between Winter and Waldmann was mutually beneficial; Waldmann gained access to a new technology that could improve Campath, and Winter found a molecule to test his technique (Marks, 2013a, Marks, 2015). The result of this collaboration was the production of a humanised version of Campath-1G, Campath-1H, in 1988 (Marks, 2013a, Marks, 2015, Waldmann and Hale, 2005).

The first human patient (suffering from NHL) tested with Campath-1H had been treated with previous versions of Campath, with some promise, but discontinued treatment due to adverse side effects (Hale and Waldmann, 2000). No observable side effects were seen in her treatment with Campath-1H, which was well tolerated and the patient showed disease improvements (Marks, 2013a, Marks, 2015). These trials showed that the improved, humanised version of Campath could have potential in a range of indications including leukaemia and lymphoma as well as in immunological disorders and the prevention of GvHD.

In summary, from the trials that had published results, the RA studies range from claiming 'significant benefit' in 7 out of 8 patients (Isaacs et al., 1992) to a 'majority' with 'symptomatic improvement' (Isaacs et al., 1996a), and 56% patients with 'clinical improvement' (Matteson et al., 1995) to 65% patients showing 'clinical response' (Weinblatt et al., 1995). The NHL studies show similar variation in results with one involving 5 patients showing no responses (Osterborg et al., 1997b) and another involving 50 patients showing 6 partial remissions and complete remission in bone marrow in 32% of patients (Lundin et al., 1998).

For CLL responses were more pronounced and at least half of patients showed a response in all trials: 1) in 9 patients there were 3 complete remissions and 5 partial remissions (Osterborg et al., 1996), 2) from 4 CLL patients there were 2 long lasting remissions (Osterborg et al., 1997b), 3) from 6 patients there were 3 partial remissions (Bowen et al., 1997), 4) in 6 patients there were 5 complete remissions (Dyer et al., 1997), and 5) in a phase II with 29 patients there were 11 partial remissions and 1 complete remission (Osterborg et al., 1997a).

When LeukoSite licensed Campath phase II results was claimed to show between 40-70% objective response rate in CLL patients who had failed front line therapy. This positive data motivated the companies to schedule a meeting with the FDA to discuss a strategy for obtaining market approval (Business Newswire 22<sup>nd</sup> July 1997).

This section has demonstrated that the uncertainty surrounding the novel approach to Campath was overcome through a process of learning within the team involved at Cambridge University. This learning continued despite the changes in licensee. This was facilitated by the smooth transferral of the project, and associated data, to LeukoSite, where Wellcome staff went 'above and beyond what they probably even had to do in order to help [LeukoSite] bring the antibody in' (interviewee C). This is important for the accumulation of tacit knowledge throughout the clinical development of a project.

Campath was central to the LeukoSite strategy, demonstrated in their 1997 annual report, the project is described as its lead product candidate (PR Newswire, 1999). During this period it has been noted (interviewee C) that there was a 'productive' and 'trusting' relationship between the academic investigators, mainly Waldmann and Coles, and the researchers and management team at LeukoSite.

On consideration of the disease-based knowledge surrounding Campath is that 16,782<sup>104</sup> articles mentioning the primary indication subclass (CLL = lymphoid) were published in the years prior to the initiation of trials (up to and including 1985). In addition there were a large number of articles published mentioning the target (around 200 publications up to when the drug was approved<sup>105</sup>), there was a relatively strong knowledge base surrounding the disease area.

This section has demonstrated that despite the novel approach applied in the development of Campath, several incremental changes and associated learning process facilitated the accumulation of knowledge. Furthermore, the consistency of the research group (as will also be discussed further below) and the good communication between organisations further facilitated this process. This justifies the score '1' for membership into the extensive and accumulated knowledge base set.

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<sup>104</sup> This figure was obtained using the Medical Subject Heading (MeSH) term 'leukemia, lymphoid' as a search term in PubMed. This is the term generated to account for Acute Lymphocytic Leukemia, and includes the subsets: 'Leukemia, B-Cell; Leukemia, Biphenotypic, Acute; Leukemia, Prolymphocytic; Leukemia, T-Cell; and Precursor Cell Lymphoblastic Leukemia-Lymphoma.

<sup>105</sup> This is compared to around 100 articles published for targets in 1990, declining to 8 per target in 1999 (Booth and Zimmel, 2004)

#### 7.2.4 Market demand (QCA score = 1)

Throughout Campath development market demand expectations varied significantly. Discovery of Campath was motivated by a desire to develop a laboratory tool to investigate immune tolerance (Marks, 2013a, Marks, 2015). However, the investigators realised that Campath could be used to treat Graft versus Host Disease (GvHD) which caused transplant rejection in bone marrow transplants (Hale and Waldmann, 2000, Clark, 2005, Marks, 2013a, Marks, 2015).

Broader applications were foreseen for the project in 1982 when the first patient, a man suffering from NHL, was treated with the murine antibody, Campath-1M (Marks, 2013a, Hale and Waldmann, 2000). Additional pilot studies were undertaken in patients suffering from leukaemia and anaplastic anaemia, showing effectiveness, tolerance and little toxicity (Marks, 2013a). In addition, the first CLL patient was first treated in 1987.

This testing of Campath was experimental, however, it also provided evidence to support drug's application to a broad range of indications. It is likely that this was the motivation for Wellcome Biotech (then a subsidiary of BW) agreeing to license the project, via the BTG, who acted as a technology transfer body to take publicly funded research through to commercialisation.

Subsequently, the project was humanised and the Wellcome license was extended to include the resultant Campath-1H (Hale and Waldmann, 2000). At this time Campath was 'expected [to] reach a much wider market and perhaps break through the 'billion dollar threshold' which big pharma are seeking' (ibid). This motivated 'a programme of trials of Campath-1H in RA (RA), leukaemia and lymphoma' (ibid). The development of trial protocols that focused on large markets, including, mainly NHL and subsequently RA (interviewee A) indicates the large potential market for Campath.

Despite Wellcome undertaking several trials (Lim et al., 1993, Matteson et al., 1995, Weinblatt et al., 1995, Osterborg et al., 1997b, Bowen et al., 1997, Isaacs et al., 1992, Isaacs et al., 1996b), developing the manufacturing technique and investing heavily (around £50m at the time) into Campath, they decided to discontinue their license in 1994 (Hale and Waldmann, 2000, Marks, 2013a, Marks, 2015). This was motivated by two things 1) the 1993/94 restructuring at Wellcome and the re-evaluation of their pipeline priorities (Pharma Marketletter, 1993c, interviewee A), and 2) the diminishing commercial potential of the project, following disappointing results in NHL and RA trials (AFX International Focus, 1994, interviewee A).



The license was returned to BTG who, based on the promising results in CLL, aimed their efforts to find another partner at smaller companies who would be more motivated by the smaller commercial potential (Marks, 2013a, Marks, 2015).

LeukoSite (US biotech) in-licensed Campath and undertook a pivotal trial in CLL leading to drug approval in 2001. LeukoSite did acknowledge the ongoing potential for Campath in larger therapeutic areas, in the form of ongoing or planned trials in multiple sclerosis and NHL (Millennium Pharmaceuticals, 1999, interviewee B). Furthermore, the company received orphan drug designation for Campath, for ‘the treatment of patients with B-cell CLL who have been treated with alkylating agents and who have failed fludarabine therapy’<sup>106</sup>. This facilitates the creation of a market in a small patient population.

Despite the long duration of the development of Campath, the main patent was not filed until 1994 (Waldmann et al., 1998) meaning that the potential to appropriate returns from the product would not expire until at least 2014, around 14 years after the approval of the drug.

As this section demonstrates, Campath was initially thought to have broad applicability, however, LeukoSite focused on gaining approval in a smaller indication initially. However, LeukoSite also recognised potential additional indications, such as multiple sclerosis, which has since become the main indication for the Campath compound, labelled Lemtrada<sup>107</sup>.

### **7.2.5 Stakeholder Perspectives (QCA score = 1)**

In addition to the commercial and scientific story of Campath, there is also a significant narrative that implicates the role of users (both patients and physicians) in the successful development of the project. This is highlighted in the early establishment of the Campath users group (Waldmann and Hale, 2005). The Campath users group was established in the mid-1980s when the trials in transplant centres began to expand, acting to facilitate access to patients for large scale trials (Hale and Waldmann, 2000).

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[www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD\\_Results\\_2.cfm?Index\\_Number=107197](http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=107197) (accessed 25/2/2015)

<sup>107</sup> Interestingly Sanofi, who took development of Campath through a series of acquisitions, withdrew Campath from the market for leukaemia patients in order to re-brand it as Lemtrada, thereby demanding a higher price from the multiple sclerosis indication [www.fiercepharma.com/story/sanofi-pulls-campath-clear-way-higher-priced-lemtrada/2012-08-21](http://www.fiercepharma.com/story/sanofi-pulls-campath-clear-way-higher-priced-lemtrada/2012-08-21).

Further participation from users was seen when Wellcome discontinued development of Campath, when Hale and Waldmann state that they were ‘becoming very concerned how to support all these groups who clearly believed that CAMPATH-1 would help their patients’ (Hale and Waldmann, 2000). This highlights the support that Campath received from patients during its course of development, an aspect which may have contributed towards its eventual success.

The role of expectations during the development of CAMPATH is also something that is commented on in the narrative written by Hale and Waldmann (2000) and Mike Clark (Clark, 2005). One issue was the decision, by BTG not to patent the early versions of Campath (Hale and Waldmann, 2000). This move is reminiscent of the attitude felt towards mabs when they were discovered in the 1970s, where the MRC and the NRDC did not think the potential immediate applications warranted patent protection (Tansey and Catterall, 1997). This hesitant expectation was clearly overcome by the time Campath-related patents were applied for in 1988 by BTG (Waldmann et al., 1998, Waldmann et al., 2003) and by Wellcome Biotech who saw substantial enough potential to enter into a licensing agreement (interviewee A).

In addition to the expectations described by the scientists’ narratives (Hale and Waldmann, 2000, Waldmann and Hale, 2005) it is also likely that public support surrounding Campath may have been influenced by the newspaper articles mentioning the drug at the time. The first newspaper articles mentioning Campath appear soon after the Wellcome license, in 1988, and it is evident from the vocabulary used that the media pick up on the excitement around the potential of the drug.

In articles found in *The Times*, *The Toronto Star* and the *Washington Post* Campath is repeatedly referred to as a ‘magic bullet’ (Wright, 1988, Reuter, 1988, *Washington Post*, 1988). Two years later the positive expectations projected in the media continue with another *Times* article about Campath headlined ‘The mission to find a killer for cancer’ (Wright, 1990). Interestingly, where ‘magic bullet’ was mentioned on several occasions in the 1980s the publications in the 1990s (of a total of 133) the term does not appear at all. In the early 1990s the drug was described as a “new wonder drug which treats leukaemia, lymph cancer and rheumatoid arthritis” (Foster, 1992), continuing the highly positive expectations felt in the early stages of the drug’s development.

In the latter half of the 1990s, newspaper articles mentioning Campath are seen more in the USA, with the acquisition of the license for Campath moving to LeukoSite. Furthermore, during this period there is a shift from articles about the drug itself towards an interest in the companies involved in the development of the drug.

In addition to the newspaper articles, the reflections and commentaries written by the researchers involved in the project also emphasise the importance of user groups, created during the trial process (Hale and Waldmann, 2000, Waldmann and Hale, 2005, Marks, 2013a, Marks, 2015).

In summary, the strong stakeholder support, mainly from the participation of users in the development of the drug, and illustrated in the positive media reports associated with the drug. This justifies the QCA score '1', indicating full membership into the set positive stakeholder perspectives.

#### **7.2.6 Organisational environment (QCA score = 1)**

Initial research into Campath was undertaken in the Pathology Department at University of Cambridge, funded by the UK's Medical Research Council (MRC). BTG had been created in 1981 from a merger of the National Research Development Corporation and the National Enterprise Board, to help in the commercialisation of academic research. As the organisation responsible for gaining intellectual property protection and commercialising scientific discoveries that arose from government funded research, the CAMPATH researchers had little option but to offer BTG a license (Marks, 2013a, Marks, 2015).

In the early 1980s BGT licensed Campath despite the NRDC's previous scepticism regarding the applicability of mabs, and the decision not to patent Campath-1 (the first product arising out of this programme of research) (Hale and Waldmann, 2000, Marks, 2015). This, and later agreements were also guided by the Cambridge University's Wolfson Cambridge Industrial Unit (set up in 1971 with money from the Wolfson Foundation<sup>108</sup>), which was set up with the purpose of fostering technology transfer (Marks, 2013a, Marks, 2015).

Due to the inexperience in commercialising discoveries and licensing agreements, the Campath lead scientists (Herman Waldmann and Geoff Hale) profess their naivety to process: "luckily we did obtain a clause allowing us to continue our own academic and clinical research with the cell lines which now belonged to BTG" (Hale and Waldmann, 2000). This was 'lucky' due to the continued incremental improvements to Campath that proved to be crucial to the development of the approved product.

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<sup>108</sup> The Wolfson Foundation is a charity established in 1955, specialising in providing funding for scientific and technological excellence.

One of the things the BTG and MRC did was to patent the humanised version of Campath (Campath-1H) (Biotechnology Newswatch, 1988, Waldmann et al., 1998, Waldmann et al., 2003). However, in a move that was described at the time to be ‘the first time in memory’ sole rights to the patent were retained by the MRC, despite their policy of open access to discoveries resulting from publicly-funded research (Biotechnology Newswatch, 1988). This is likely to have been motivated by the loss of exclusivity over UK academic inventions by BTG (NRDC) in 1985 due to the failure to patent mabs (Owen and Hopkins, 2016).

Initially BTG’s commercialisation strategy targeted Celltech, who, at that time had the most experience in mabs in the UK. Despite two years of negotiations, no agreement was reached (Marks, 2013a, Marks, 2015, Hale and Waldmann, 2000). However, in 1985 Wellcome Biotech, a subsidiary of the Wellcome Foundation Ltd (later Wellcome PLC, the UK arm of BW, a large pharmaceutical company at the time) licensed the molecule (Marks, 2013a, Marks, 2015). The Cambridge scientists were pleased with this: ‘as at that time the company was one of the leading British companies in biotechnology and had the strong expertise in the large-scale production of cell cultures necessary for any scaling-up of alemtuzumab’ (Marks, 2013a, Marks, 2015).

Wellcome Biotech was a small biologics company based on Wellcome’s mature vaccine business (Pharma Marketletter, 1993c, interviewee A). Despite being a subsidiary of the larger entity, Wellcome PLC, Wellcome Biotech was a relatively autonomous, ‘semi-independent entity’ (interviewee A). Initially Wellcome Biotech had high hopes for antibody technology and were interested in developing capabilities in this area: “they [Wellcome Biotech] were far-sighted enough to want to get into therapeutic antibodies... that was going to be the new future”, building on their existing protein therapeutics and vaccine pipeline (interviewee A).

When Campath was humanised BTG were concerned that the development of Campath-1H would compromise Wellcome Biotech’s Campath-1G development (Hale and Waldmann, 2000). In response the Wellcome license was extended to include CAMPATH-1H. When Wellcome Biotech began research into CAMPATH-1H it was “expected [to] reach a much wider market and perhaps break through the “billion dollar threshold” which big pharma are seeking” (Hale and Waldmann, 2000). Therefore, Wellcome abandoned work on previous Campath projects and “started a programme of trials of CAMPATH-1H in RA, leukaemia and lymphoma”.

Up to the late 1980s Waldmann’s team were responsible for producing Campath in their laboratory (Marks, 2013a, Marks, 2015). However, it was necessary to scale up the

manufacturing technique due to the demand for the drug in trials (Hale and Waldmann, 2000, Marks, 2013a, Marks, 2015). In response the Therapeutic Antibody Centre (TAC) opened in 1990 after three years of planning (Hale and Waldmann, 2000, Marks, 2013a, Marks, 2015).

The TAC was responsible for the production of CAMPATH for trials. '[Waldmann and Hale] wanted to liberate clinical research from the bottleneck of pilot scale production' (Hale and Waldmann, 2000). The TAC was funded initially by the MRC and the Wellcome Foundation, with further support from the MRC, annually (£200,000) for five years, along with funding from Wellcome Biotech and Cambridge University (Hale and Waldmann, 2000, Marks, 2013a, Marks, 2013b). In 1996, Waldmann also gained support for the TAC from Tim Springer, who had just founded a new US biotechnology company, LeukoSite (Hawkes, 1996). The TAC was key to the development of Campath in providing the facilities necessary to manufacture enough molecule for trials.

Over the seven years that Wellcome Biotech was involved in Campath, the company invested over £50m and contributed towards the establishment of a more efficient manufacturing technique (Hale and Waldmann, 2000, Marks, 2013a, Marks, 2015). However, in 1994, Wellcome discontinued the license for Campath which reverted to BTG (Marks, 2013a, Marks, 2015).

Despite the willingness of Wellcome to see the potential in antibodies the technology was still, in the late 1980s and early 1990s, a new and risky avenue to take: 'I guess it wasn't clear that therapeutic antibodies were going to be as big as we know they are today and so there was the element of risk there' (interviewee A). This is echoed by observers from the University of Cambridge: 'Many people were very sceptical in the mid-1980s about the commercial future of antibodies and other biotech drugs but Wellcome was excited by the potential of this new area', comments from Dr Richard Jennings, Director of Technology Transfer and Consultancy Services, Cambridge Enterprise Ltd (University of Cambridge, 2009).

In addition to the risk associated with the new technology, in 1994 Wellcome Biotech underwent an organisational shift when it was re-absorbed into the parent organisation, Wellcome PLC (Marks, 2013a, Marks, *forthcoming*). This had a detrimental effect on the academic scientists working on Campath-1H, as Hale and Waldmann comment: 'although Campath-1H continued to be developed, and we enjoyed a productive relationship with many of the Wellcome scientists, the ultimate decisions were removed

to a level beyond our access, and trial protocols were developed with a focus on large markets, starting with NHL and subsequently RA<sup>109</sup> (Hale and Waldmann, 2000).

From the Wellcome Biotech perspective one informant observes:

“for Wellcome Biotech Campath and therapeutic antibodies and the relationship with Hermann [Waldmann] was very important because it represented the future of Wellcome Biotech that was the most important thing they were doing. But when they [Wellcome Biotech] became part of the Wellcome Foundation, it was no longer the number one priority because there was a whole portfolio of other things and so it slipped down the pecking order and also there wasn't a dedicated management that was going to promote it in the way that it had been in Wellcome Biotech and so consequently, the people that were managing the portfolio didn't have the same sort of vested interest and probably didn't have the same insight or knowledge that the people at Wellcome Biotech had had.” (interviewee A)

Efforts to find a new licensee for Campath was challenging due to the negative effects associated with the discontinued license, whereby other potential licensees may wonder why the drug was unattractive (Marks, 2013a, Marks, 2015). However, BTG realised that a potential avenue for a drug in a niche indication, such as Campath in CLL, was to focus on a small biotechnology. This was based on the assumption that small companies would be more motivated by smaller commercial markets than big pharma (Marks, 2013a, Marks, 2015). Furthermore, small biotech firms are easier for academic labs to collaborate with. As Hale and Waldmann (2000) reflect: ‘in our experience it has been very much easier to interact with small biotech companies where the ethos is more akin to our academic culture and the management is closer to our level’.

It was actually Waldmann who found a licensee in LeukoSite through his connection in Tim Springer (Marks, 2013a, Marks, 2015, interviewee C). LeukoSite was founded in 1993 to commercialise Springer's work with Waldmann in the 1970s at the Laboratory of Molecular Biology at Cambridge (Marks, 2013a, Marks, 2015, Hale and Waldmann, 2000). At this time Springer had worked on the discovery of leukocyte adhesion molecules<sup>110</sup>, providing the focus for LeukoSite (Hale and Waldmann, 2000) Furthermore, Waldmann sat on the LeukoSite scientific advisory board, and the company had already

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<sup>109</sup> This is echoed by interviewees

<sup>110</sup> Leukocyte (white blood cells) were targeted in order to inhibit their disease-promoting actions, with potential in cancer, autoimmune and viral diseases ([www.rhoventures.com/healthcare-Leukosite](http://www.rhoventures.com/healthcare-Leukosite))

invested US\$1m to the relocation of the TAC to Oxford in 1994 (Marks, 2013a, interviewee C, Marks, 2015)

The agreement was risky for LeukoSite (Marks, 2013a, Marks, 2015), as Hale and Waldmann (2000) observe:

‘Chris Mirabelli took a bold risk when he committed a substantial proportion of the new company’s start-up capital towards the construction and running of a new centre for an academic group on the other side of the Atlantic... As our hope was fading that BTG would find a new licensee, LeukoSite became persuaded that CAMPATH-1H was a genuine opportunity and even though its first application (in CLL), might be outside their original remit’.

However, the licensing agreement was also strategic for LeukoSite. Firstly, a smaller indication, such as CLL, was easier and therefore cheaper for a small company, like LeukoSite, to develop and get approved (interviewee B). Furthermore, the project was synergistic with LeukoSite’s existing technological capabilities (interviewee C) and facilitated LeukoSite’s desire to enter into the antibodies sphere, which is also evident in their 1996 TAC investment (Hawkes, 1996). Here LeukoSite ‘developed drugs to block disease promoting actions of white blood cells, with potential applications within the areas of cancer, autoimmune and viral diseases’ (Rho Ventures, Perseus LLC). In addition, LeukoSite were aiming to float on the stock market, for which they needed late stage products, such as Campath, as part of the package to impress investors (interviewee C).

Despite the strategic benefits of Campath for LeukoSite’s the firm was inexperienced in bringing an oncology drug to market, motivating the establishment of a joint venture with ILEX Oncology (Hale and Waldmann, 2000, Waldmann and Hale, 2005, interviewee B and C). ILEX Oncology, founded 1994, was headquartered in Texas, USA and had experience in developing oncology projects (e.g. its lead molecule mitoguazone<sup>111</sup>) and collaborating with other firms (Marks, 2013a, Marks, 2015, Business Wire, 1997b).

As part of the BTG/LeukoSite licensing agreement with BTG LeukoSite (and ILEX) had the opportunity to develop the drug for broader indications subsequent to its approval in

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<sup>111</sup> Despite the development and application for marketing, the FDA did not approve it for AIDS-related NHL.

CLL (Marks, 2013a, Marks, 2015). This was a strategy that they did pursue and, in 1999, trials were ongoing or planned in NHL and multiple sclerosis (PR Newswire, 1999).

This section has shown that despite the disruption caused by the license discontinuation by Wellcome, key individuals (mainly Waldmann in this instance) used their networks to find a new partner. This helped the project recover and continue smoothly. Campath was strategic for LeukoSite both in therapeutic area and in its role in readying the firm for stock-market floatation. Furthermore, the lack of capabilities of LeukoSite in oncology drug development was overcome by the initiation of the ILEX Oncology Joint Venture. These factors contribute towards the QCA score of '1'.

### **7.2.7 Campath Conclusion**

In summary, several factors played a role in determining the success of Campath, overcoming issues contributing towards project drag and the Wellcome license discontinuation. Firstly, the collaboration between commercial partners, academic scientists and physicians was an important dynamic valued by those involved. Furthermore, the small biotech firm culture (in both Wellcome Biotech and LeukoSite) is more conducive to academia-collaborations, facilitating a productive environment between researchers involved.

In addition, the consistency of the CAMPATH research group influenced the productivity of the project due to the accumulation of tacit knowledge aiding development and incremental innovations. The potential market size of the drug project also played a role in its development, as demonstrated by the discontinued license by Wellcome. However, this mainly led to a delay where LeukoSite subsequently in-licensed the project. Campath demonstrated a case where research scientists, physicians, and managers retained a positive perspective around the ability for the project to yield a safe and effective drug for leukaemia.

Low potential market demand was overcome by high expectations, from user groups and physicians, despite the uncertainty surrounding antibody technology (interviewee A). However, low market potential did not persist, with broader potential in further indication being realised during development. Furthermore, public funding by the MRC enabled a substantial amount of research to be undertaken without relying on industrial partners.

## **7.3 Gemtuzumab Ozogamicin – Benefit/Risk Sharing**

Despite the categorisation of gemtuzumab (anti-CD33 MAb, CDP-771, CMA-676, Mylotarg, P-67) as a project initiated in a biotech firm (Celltech), the case shows similarities with plevitrexed. In this Celltech, like ICR, undertook much of the initial work



in discovery stages, with American Cyanamid (AC) taking on development when the project reached the clinic. However, the difference, lies in the profit- and cost-sharing agreement in gemtuzumab, as well the equity stake AC held in Celltech. This indicates that Celltech's role in the gemtuzumab was more involved, than ICR in the case of plevitrexed.

The issues facing gemtuzumab were: 1) low market potential, 2) novel and uncertain market, 3) novel and uncertain knowledge, 4) requirement of knowledge sharing between organisations in the Celltech/AC collaboration, and 5) vulnerability on Celltech's part, to external industrial dynamics. Despite no key individual(s) the project did benefit from a productive relationship between Celltech and AC, facilitated by direct CEO interaction, and the mutual benefit of the project to both firms. This interaction facilitated the sharing of expectations, in a similar process to the activity of key individuals in the cases of nelarabine, Campath and temozolomide. Furthermore, for Celltech, gemtuzumab was a test bed opportunity providing proof of concept for the novel antibody-drug conjugate approach. It is likely, although not evidenced, that this aim for proof of concept, and positive expectation, was shared by AC due to the close working relationship between the two firms.

In addition, the organisational environment surrounding gemtuzumab was facilitatory rather than inhibitory. Here, Celltech was a newly established firm benefiting from the hype characteristic of the UK biotech industry, in the early 1980s. Furthermore, AC was a more established, well known and profitable chemicals company that was not subject to the vulnerabilities seen in smaller firms.

### **7.3.1 Interview sources**

Interviews were carried out with two individuals, interviewee I and interviewee K working at Celltech during the development of gemtuzumab.

### **7.3.2 Introduction**

Gemtuzumab is an antibody conjugate<sup>112</sup> comprising a humanized MAb, targeting the CD33 antigen, and the cytotoxic agent, calicheamicin, isolated from *Micromonospora echinosporo*. The project began clinical development in the early 1990s, through a

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<sup>112</sup> Some distinguish between antibody-drug conjugates and antibody-toxin conjugates by only terming the latter as immunotoxins (Teicher and Chari 2011), however, others (including the Pharmaprojects database and Appelbaum 1999) use 'immunotoxin' to refer to both. In this thesis the distinction will be made, however, the similarities between the two approaches should also be appreciated.

collaboration between AC (USA) and Celltech (UK), and received approval in 2000 for the treatment of patients suffering from AML.

<b>1984</b>	CD33 antigen identified
<b>1985</b>	AC/Celltech agreement signed
<b>1987</b>	Calicheamicin discovered in Texas
<b>1989</b>	First immunotoxin (anti-CD25 single chain Fv and <i>Pseudomonas exotoxin</i> ) produced
<b>1994</b>	AC acquired by American Home Products (Wyeth)
<b>1995</b>	Gemtuzumab Phase I/II trial initiated in USA
<b>1997</b>	Phase I/II trial data reported; Pivotal Phase II/III trials initiated
<b>1998</b>	Gemtuzumab Phase III trial preliminary results reported
<b>1999</b>	NDA submitted
<b>2000</b>	Gemtuzumab approved; Orphan drug status approved in Europe

**Table 26 Key events in development of gemtuzumab**

### **7.3.3 Knowledge base (QCA score = 0)**

The knowledge base contributing towards the development of gemtuzumab can be traced to a discovery collaboration between the large US company, AC and a small UK biotechnology firm, Celltech.

The discovery and early development of gemtuzumab involved identifying and combining three components, the mab targeting the CD33 antigen, the drug/toxin (in this case calicheamicin), and the linker. It is necessary that the linker is designed to be sufficiently stable not to release the drug into the body unpredictably, but weak enough to release the drug when antibody-antigen binding occurs on the tumour cell.

Research surrounding the antigen target, CD33, goes back to 1987, when one publication mentioned that it was 'potentially useful for myeloid leukaemia' (van der Schoot et al., 1987). In addition, the specificity of CD33 to haematological malignancies was quantified as being present in 65-80% of myeloblastic patients (Caron and Scheinberg, 1994). By 2005 85-90% of AML cases were found to be CD33 positive (Linenberger, 2004). The well-researched nature of the drug target, CD33, is further

exemplified in a search for associated publications<sup>113</sup>, wherein 566 articles were found prior to, and including the year gemtuzumab entered clinical trials (1995).

Despite this, and other research linking antigens to haematological malignancies (Griffin et al., 1984, Dinndorf et al., 1986), in 2004 one haematologist doubted the clinical significance of CD33 expression claiming that more research is needed (Linenberger, 2004) It was Bernstein, at the Fred Hutchinson Cancer Research Center who led the CD33 target research directly contributing to the discovery of gemtuzumab. In this research Bernstein and colleagues (Bernstein et al., 1987, Bernstein et al., 1992) wanted to identify differentiation markers in myeloid cells.

Serendipity was involved in the discovery of the drug conjugate, whereby calicheamicin was identified from a soil sample by scientists at Wyeth (AC) in the mid-1980s (Maiese et al., 1989, interviewee K). Upon isolating and investigation, the compound was found to have potent anti-tumour and anti-microbial activity (ibid). However, calicheamicin was too toxic to be useful as a monotherapy in cancer treatment (Bardi, 2001)

To facilitate the use of calicheamicin as an anti-tumour agent, it was necessary to conjugate an antibody to the toxin to infer toxicity whilst targeting the CD33 antigen (interviewee I). A suitable antibody, P67.6, was found to also have the additional advantage of being rapidly and efficiently internalised into the cells expressing the CD33 antigen (Hamann et al., 2001, Hamann et al., 2002). This conjugate was complemented in the collaboration between AC, who were developing calicheamicin production capabilities, and Celltech, who had antibody capabilities (Maiese et al., 1989), and the Fred Hutchinson Cancer Research Center, who had been working on CD33 and associated antibodies (Bernstein et al., 1987, Bernstein et al., 1992, Hamann et al., 2001, Hamann et al., 2002). However, this antibody was a mouse antibody requiring humanisation due to expected issues of immunogenicity.

The introduction of mab technology, to target antigens, can be traced back to 1975 and the seminal work of Kohler and Milstein (Kohler and Milstein, 1975). Much of the work at this time was being carried out in the UK in Cambridge at the Medical Research Council-funded Laboratory of Molecular Medicine, run by Milstein. In the early 1980s Celltech was working with the UK's Medical Research Council (MRC) and had adopted

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<sup>113</sup> Search term used: (CD33) AND ("1900/01/01"[Date - Publication] : "1995/31/12"[Date - Publication])

capabilities in humanising mabs. Celltech were responsible for this task (humanisation) in the development of gemtuzumab (interviewee I).

One of the major issues at this time was how to link the calicheamicin toxin and antibody. Researchers at both AC and Celltech worked to resolve this problem. This was time-consuming due to the tendency for the 'linker', responsible for attaching calicheamicin and the antibody, to reduce the activity of the humanised antibody (interviewee K).

Preclinical studies were undertaken indicating efficacy with minimal toxicity in solid and liquid tumours (Pharmaprojects). In 1994 phase I/II trials began in AML patients, with an expectation that the Product License Application would be filed in mid-1997 (Pharma Marketletter, 1993b). In the 1995 Celltech annual report initial results indicated that there were no significant side effects, gemtuzumab was well tolerated (Celltech Group PLC, 1995).

By the 1996 annual report, the first stage of the phase I/II trial was complete, concluding that the drug was well tolerated, with 2 complete responses and 3 partial responses, from a total of 36 refractory AML patients (Celltech Group PLC, 1996a, London Stock Exchange Aggregated Regulatory News Service, 1996). These were described as "encouraging" results of a "bullet type" drug, in the media (Extel Examiner, 1996). Of particular importance was the drug's remarkable safety profile, compared with the high toxicities seen in the alternative AML therapies, which were often associated with death (Celltech Group PLC, 1996a).

In response to these results, the second stage was planned to recruit 50 relapse patients over 10 US and Canadian centres (Celltech Group PLC, 1996a, London Stock Exchange Aggregated Regulatory News Service, 1996). It was expected that these trials would be used to support accelerated registration of the product (ibid). In addition, a European arm of the trial was planned (Celltech Group PLC, 1996b), as well as trials in other indications including ovarian (later initiated in 1997) and lung cancer (Extel Examiner, 1996).

One phase II trial in 59 AML patients showed 36% of patients in remission, with an additional two supporting phase II showing closely comparable results of 36-44% remission rates (reported in 1999) (Celltech Group PLC, 1999). Despite these response rates being comparable to standard combination chemotherapy regimens, the improved safety profile provided sufficient evidence to support FDA accelerated approval for the treatment of patients age 60 or older with CD33 positive relapsed AML (Celltech Group PLC, 2000).

In 1998 reports indicated that a relatively small number of patients, just over 90, were ever treated with gemtuzumab in trials (Durman, 1998). From the FDA documentation upon submission a total of 156 patients<sup>114</sup> are shown to have been treated with the drug, representing a small number providing the evidence base for approval.

The novelty described in this section is mainly represented in the knowledge surrounding the target and how this relates to the drug and disease pathway. However, knowledge base for the primary indication was extensive, with 19,424<sup>115</sup> publications found in the years leading up to gemtuzumab trials (up to and including 1993).

In conclusion, the development of gemtuzumab involved a range of novel ideas, technologies and compounds accompanied by a high level of uncertainty. Difficulties were encountered, for instance, with the design of the linker molecule, demonstrating these uncertainties. This indicates that a relatively low level of accumulated, learned knowledge would have been ascertained during clinical development of the drug. This justifies the QCA score of '0'.

#### **7.3.4 Market demand (QCA score = 0)**

As with most antibodies, the indications gemtuzumab could be applied to were limited by the specificity of the target antigen. In this case CD33 was known to be present on certain leukaemic cells, with 65-80% of myeloblastic leukaemia patients showing expression of the antigen (Caron and Scheinberg, 1994, interviewee I). This presents a small potential market demand for gemtuzumab where it would only be applicable to certain types of myeloblastic leukaemia.

Preclinical development of gemtuzumab was undertaken in both solid and haematological tumours (Pharmaprojects) with higher efficacy found in haematological malignancies. All subsequent trials were carried out in AML, and included paediatric and adult patients (Sievers et al., 1998, Sievers et al., 1999a, Sievers et al., 1999b, Sievers et al., 2000, Voliotis et al., 2000, Leopold et al., 2003, Appelbaum, 1999, de Vetten et al., 2000). In 1993, AML incidence was around 35,000 new cases per annum with 80% relapse rate in the first 18 months in surviving patients (Pharma Marketletter, 1993a). Furthermore, AML treatments at the time were limited to non-specific cytotoxins that were highly toxic with severe side effects.

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<sup>114</sup> [www.accessdata.fda.gov/drugsatfda\\_docs/nda/2000/21174\\_MYLOTARG\\_medr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21174_MYLOTARG_medr.pdf)

<sup>115</sup> This figure was obtained using the Medical Subject Heading (MeSH) term 'Leukemia, Myeloid, Acute' as a search term in PubMed.

Despite the rare cancer primary indication and associated small market potential, gemtuzumab development fulfilled the Celltech strategy emphasising areas of unmet need. As per their 1993 annual report: 'Celltech concentrates on those diseases where there is both an unmet medical need and either a large patient population or prospects for reducing mortality significantly' (Celltech Group PLC, 1993). This strategy is also associated with the potential for achieving high prices: 'if CDP771 [gemtuzumab] can demonstrate a significant increase in life expectancy, it could gain wide market acceptance despite a high price', considering alternative AML treatments at that time were expensive and ineffective (ibid). Furthermore, competitors in AML were scarce: 'ImmunoGen and Protein Design Labs, are in early clinical development with conjugates which target the same antigen as CDP771'. However, they also claim that gemtuzumab was distinctive due to its novel approach involving an antibody and proprietary cytotoxic drug, calicheamicin (Celltech Group PLC, 1993).

The gemtuzumab market potential was quantified in media reports. In early years of the collaboration between AC and Celltech the market for mab-based products was expected to be valued at \$300m or around 15% of a \$2bn market by 1995 (PR Newswire, 1986). For instance, in the year prior to approval of gemtuzumab sales were predicted to stand at \$250m within four years (Durman, 1999). Another estimate presented expected annual earnings to be at least \$150m (The Independent, 1999). Despite these estimations motivating industry analysts to recommend investment into Celltech as a "strong buy" (Durman, 1999) they do not present gemtuzumab as a potential blockbuster. This indicates a limited market potential for gemtuzumab despite its orphan drug status granted in Europe in the same year the project was approved 2000 (Pharma Marketletter, 2000b).

This section has shown that gemtuzumab was developed for a small patient population, (limited by its CD33 target) and press reports claiming that the drug would achieve relatively low revenue status. This is despite the potential for gemtuzumab to command a high price and the granting of orphan drug status. This justifies the '0' QCA score.

### **7.3.5 Stakeholder Perspectives (QCA score = 1)**

Expectations of gemtuzumab, from the scientific investigators at the organisations involved in discovery and development, were high (interviewees I and K). This is influenced by the novelty of the technology area, where immunotoxins and antibody-drug conjugates presented a new strategy (Pastan, 2003).

Furthermore, firm expectations of the project were high. In particular, Celltech anticipated that gemtuzumab was going to be their first clinical project, at a time when they were

expecting to expand into drug discovery and development, as opposed to their previous focus on provision of contract research services (interviewee I).

In addition, newspaper articles report at least three patient stories which contribute towards a positive public perception of the drug. For instance in 1999, a patient receiving the drug as part of a trial garnered support, in the form of donations, to pay for continued treatment after funding was refused (Minnecci, 1999). Another story reports a plea for support from the public to pay for transportation and treatment of other medical problems, by a couple whose son, suffering from AML, was being treated with gemtuzumab (Thompson, 2000). The final patient story in 1999 reported an 11 year-old boy who had qualified for treatment on a gemtuzumab trial (United Press International, 1999).

All of these reports appear in newspapers and serve to provide a positive public perception for gemtuzumab, where patients are desperate to keep receiving treatment of the yet unapproved drug. In addition to public and industry support for the drug, the fact that it received accelerated approval also indicates that the FDA had high expectations that the drug would fulfil a previously unmet need. These factors justify the membership of the project into the set positive stakeholder perspective and therefore the QCA score '1'.

### **7.3.6 Organisational environment (QCA score = 1)**

The development of gemtuzumab began with a three-way collaboration involving AC an established US manufacturing firm, the Fred Hutchinson Cancer Research Center, a well-known and respected US research institute, and Celltech, a small UK biotechnology company founded in 1980 and specialising in antibody drug discovery and development. The collaborations came together through the discovery of gemtuzumab, however AC (Subsequently American Home Products, then Wyeth) was responsible for clinical development. The collaboration between AC and Celltech began before the identification of gemtuzumab as a potential cancer drug. This collaboration came in the wake of the 1981 proclamation that AC was increasing R&D in therapeutics, particularly in arthritis and oncology (Chemical Week, 1981), with an increasing in R&D, in 1983, by 10-15% (Chemical Week, 1983). This implies that AC were focusing down more on oncology and investing substantially into increasing their R&D activities, including in the development of gemtuzumab.

The Celltech/AC collaboration, initiated in 1986, initially involved 3 compounds, including gemtuzumab, on a contract research basis involving 3 compounds (interviewee I, PR Newswire, 1986, Pharma Marketletter, 1995a). This agreement was 'to develop a new approach to antibody cancer imaging and therapy using "second generation" mabs...

Celltech will design purpose-built molecules which will “engineer-out” the undesirable characteristics of the mab and its linked agent’ (PR Newswire, 1986). At this time Celltech’s network of UK and US scientists was an important factor in attracting AC (Celltech Group PLC, 1986b). Furthermore, the AC Deputy Managing Director, David Lilly comments:

“Celltech’s pioneering approach will reinforce our work in cancer therapy, leading to products that should be more precisely targeted and hence more efficacious and with fewer side effects than today’s treatments. The research and development capability from the agreement, coupled with our proven marketing skills, will ensure commercial success of this venture” (Celltech Group PLC, 1986b)

This agreement entailed £5m funding from for initial research for 2 years, minimum, with provision for continuing work, licensing fees and royalties (Celltech Group PLC, 1986a). At this time AC were big players in the chemicals market with over 2,500 products and 1985 sales of \$3.53bn (Celltech Group PLC, 1986a). Furthermore, the UK R&D arm of AC, Lederle Labs, had extensive experience of developing cancer drugs including methotrexate, vincristine and cisplatin, accounting for over half of the overall spending on R&D of the parent company, amounting to \$200m (Celltech Group PLC, 1986a).

When Peter Fellner joined Celltech as CEO, in 1990 the terms of the agreement were renegotiated, with Celltech becoming a more active partner and the introduction of a cost-sharing aspect between the two companies (interviewee I). This built on Celltech’s capabilities in antibodies, established through collaborations with the MRC (interviewee I) and reflected the desire, by the Celltech board, to expand into drug discovery and development (ibid). At this point AC wanted to give Celltech an opportunity to manage the project and gain leadership experience in the discovery and development of an oncology drug, and AC wanted to learn from a newer biotechnology company, Celltech (interviewee I).

In addition, Celltech was using gemtuzumab as a test bed for adapting the technology more widely in other types of cancers. The project was described as ‘very important as a test of Celltech’s research in turning human antibodies into drugs’ (Clark, 2000). In addition, a failure of another Celltech drug in the portfolio, in 1997 (described as an “annus horribilis”), implied that the success of gemtuzumab was critical to the survival of the company (Pharma Marketletter, 1997b, Pharma Marketletter, 1997a).

Another aspect contributing to the project’s success was the close cooperative relationship between the two CEOs (at Celltech and AC) (interviewee I). In addition, the Celltech’s organisational environment was positive, involving an ‘inclusive management



style', with young researchers working in a creative and encouraging culture (interviewee I). These interpersonal factors would be expected to have a significant positive effect on the development gemtuzumab.

Celltech leadership of the project continued until the completion of discovery and preclinical work, at which point clinical development passed to AC. At this time (in 1994/95) AC was acquired by American Home Products (later Wyeth). This move was associated with a distancing between them and the clinical team in the USA (interviewee I). Furthermore, upon acquisition AC lost around 300 employees (Pharma Marketletter, 1994). However, American Home Products were described as being motivated by a desire to increase their medical pipeline (Randall and Fix, 1994), with the chairman, John R Stafford, stating that the merger would allow them to 'strengthen its role in cancer drugs' (Freudenheim, 1994), indicating a strategic role of gemtuzumab despite the merger. This is echoed by interviewee K where an appreciation of the project by the acquiring company is observed. Furthermore, a Celltech representative remained present on the clinical committee for gemtuzumab.

The AC and Celltech collaboration represents strong inter-organisational synergy, and a mutually beneficial relationship. This was supported by the profit/cost-sharing nature of the agreement and the equity investment AC had in Celltech. In addition, the level of interpersonal contact, and cooperation also had a significant positive effect on the development and progression of gemtuzumab. Each firm had its own internal motivation for enabling the uninterrupted development of the project, driven in part by expectations about the technology, but also about favourable strategies. For these reasons gemtuzumab has membership into the set supportive organisational environment, scoring '1' in QCA.

### **7.3.7 Gemtuzumab Conclusion**

The low expectation of the potential market for gemtuzumab and the novelty of the knowledge base supporting its development were overcome by three main factors. Firstly, the high expectations of the drug and the new technological modality it implemented. Secondly, the effective and productive collaborative environment that surrounded development and thirdly the ambition for the drug to provide proof of concept for the therapeutic approach. These conditions surrounding the project clearly contributed towards the successful outcome of gemtuzumab.

## **7.4 Banoxantrone – Moving Organisations with Different Priorities**

Banoxantrone (AQ4N) development arose from a collaboration between a lab at Leicester Polytechnic/De Montfort University and BTG, who were, at the time, responsible for commercialising university technology. Banoxantrone initially benefitted from BTG funding, high potential market demand, high expectations, and a supportive academic research team.

However, issues contributing towards the demise of the project included: 1) difficulties in knowledge transfer between organisations and lack of molecular understanding of the drug's mechanism of action, 2) the need to combine the drug with radiation and the implication of this on market demand, 3) lack of user support due to an unusual patient side-effect, 4) AZ and KuDOS lack of organisational and strategic fit, and 5) vulnerability of small firms to industry dynamics.

When the project passed to KuDOS communication and coordination breakdown between industry partners and the academic team, and banoxantrone was no longer prioritised. In response KuDOS out-licensed, initially North American rights, with worldwide rights following, to Novacea, a US company. Initially this was a positive development for the project. However later Novacea was forced to merge with Transcept due to a failure of another project in their portfolio, and thereby returned the banoxantrone rights to BTG.

These factors not only contributed towards project drag and eventual termination of the project but we also observe the breakdown of protected spaces upon the Novacea/Transcept merger. As highlighted in this case history collective expectations surrounding the project were positive while at Novacea, however, the re-evaluation of the project upon acquisition, arose from a breakdown of these uncovered the accumulated project drag, and subsequent termination.

### **7.4.1 Interview sources**

Interviews were carried out with individuals involved in the drug discovery and development process, email correspondence Y and interviewee H.

### **7.4.2 Introduction**

Banoxantrone is a prodrug developed to treat brain cancer. Discovered by a research team at Leicester Polytechnic/De Montfort University, banoxantrone was licensed to KuDOS (later acquired by AZ) subsequently passing to Novacea. Banoxantrone was discontinued in 2008 when Novacea was acquired by Transcept.

<b>1990</b>	BTG license to fund development of banoxantrone
<b>1991</b>	First anti-cancer patents taken out mentioning Patterson as inventor
<b>1993</b>	First publication mentioning AQ4N (banoxantrone) by Patterson
<b>1996</b>	Carmustine implant approved as adjuvant therapy for glioma patients
<b>1998</b>	BTG initiate banoxantrone Phase I trial with Cancer Research UK
<b>1999</b>	Approval of temozolomide for recurrent glioblastoma
<b>2001</b>	NICE approval of temozolomide
<b>2002</b>	KuDOS license of banoxantrone from BTG
<b>2003</b>	North American rights licensed to Novacea (by KuDOS)
<b>2004</b>	Additional Phase I carried out by Novacea
<b>2006</b>	KuDOS acquired by AZ
<b>2007</b>	Novacea expand license to worldwide rights; ALL Phase II initiated by Novacea
<b>2008</b>	Novacea merges with Transcept; AQ4N is discontinued

**Table 27 Key events in development of banoxantrone**

### **7.4.3 Knowledge Base (QCA score = 0)**

Banoxantrone is a prodrug activated in the presence of low oxygen levels (hypoxic) in tumour cells. The existence of hypoxia in tumours was first suggested by researchers in the 1950s (Thomlinson and Gray, 1955). Early research demonstrated that hypoxic regions of tumours are resistant to radiotherapy and some chemotherapies, highlighting an area of unmet need in cancer therapeutics (Singh et al., 2008). It was not until the 1970s that prodrugs were designed to be hypoxia-activated, to produce a cytotoxin (Lin et al., 1972, McKeown et al., 2007).

This stream of research was picked up by Laurence Patterson. As a PhD researcher, Patterson had studied the deactivation of drugs through drug metabolism, before working in the pharmaceutical industry on the safety of drugs, returning to academia the School of Pharmacy at Leicester Polytechnic (later, De Montfort University) (interviewee H). Patterson's multi-disciplinary team of researchers went on to identify AQ4N (banoxantrone), the first anticancer molecule in the anthraquinone class of bioreductive agents (McKeown et al., 2007).

Prior to this the only other bioreductive agent progressing clinically, was tirapazamine, a benzotriazine derivative which had entered trials in the USA in 1994 (Doherty et al., 1994, McKeown et al., 2007). Despite tirapazamine seemingly providing a potential competitor, it was not perceived as a threat by the inventors due to the distinct difference between the two classes of compounds. Banoxantrone was distinct from tirapazamine due to the migration of effects of the bioreduced active drug to cells adjacent to those in the hypoxia region (interviewee H). Furthermore, tirapazamine provided proof of concept for banoxantrone, commercially and scientifically justifying the project (interviewee H).

Banoxantrone acted through its reduction, under hypoxic conditions, to the cytotoxin, AQ4, an analogue of mitoxantrone, the commonly used chemotherapeutic, (first approved AML in 1987 (Fox, 2004). Mitoxantrone acted to inhibit topoisomerase II, disrupting cell division and DNA synthesis and repair (McKeown et al., 2007). Additional drugs previously approved targeting topoisomerase II target include commonly used cytotoxins such as etoposide (FDA approved pre-1984), doxorubicin (FDA approved pre-1984), and daunorubicin (FDA approved in 1987) (Hande, 2008). This demonstrates validation of the banoxantrone target and is further supported wherein 1,905 articles were found mentioning 'topoisomerase'<sup>116</sup> prior to, and including the year banoxantrone entered clinical trials.

Whilst topoisomerase II inhibitors were efficacious, the high levels of normal tissue toxicities they produced was problematic (ibid). By specifically targeting tumour cells in hypoxic regions, banoxantrone overcame toxicity issues whilst maintaining efficacy.

Banoxantrone preclinical studies were funded by BTG, with additional animal model research undertaken by Stephanie McKeown and David Hirst at the University of Ulster, funded by the Ulster Cancer Foundation and the CRC (e.g. (Patterson, 1993, McKeown et al., 1995, Hejmadi et al., 1996). These studies showed that the drug was 'significantly better in their experimental systems than the leading drug in the USA tirapazamine' (1998). At this time the scientists working on banoxantrone had high expectations of the project describing the work as 'potentially a major breakthrough' (McIntyre, 2001).

In 2001 (the year prior to the KuDOS license) in response to encouraging preclinical toxicology results a phase I trial was initiated in oesophageal carcinoma patients (BTG, 2001). Funded by BTG, organised by the CRC, this trial took place at Leicester Royal Infirmary and the Imperial Cancer Research Fund's unit at the Churchill Hospital, Oxford (ibid). This trial showed favourable pharmacokinetics, with the drug being well tolerated and no drug-related adverse events reported (Steward et al., 2007). In 2004 Novacea initiated additional phase I trials, in the USA, in a range of solid tumours and NHL (Papadopoulos et al., 2008). These demonstrated that maximum tolerated dose and dose-limiting toxicity had not been reached at the maximum administered dose of 480mg/kg (ibid), over twice the dose required to elicit a response in human tumours

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<sup>116</sup> Search term used: ("topoisomerases") AND ("1900/01/01"[Date - Publication] : "1998/31/12"[Date - Publication])

xenografted in mice (interviewee H). Additional trials were undertaken in 2006 for glioblastoma and in 2007 for ALL (Novacea, 2007b, Novacea, 2006b).

During the period 2003-2007 separate development plans were undertaken in the UK (KuDOS/AZ) and USA (Novacea), however, these fed into each other in the form of a data sharing agreement. By 2006, four phase I trials had been completed showing that banoxantrone was well tolerated in solid and B-cell malignancies (Novacea, 2006a). These trials also validated the banoxantrone mechanism of action, with activated AQ4 found in hypoxic tumour regions and a direct relationship observed between levels of tumour hypoxia and the concentration of active drug (Albertella et al., 2008). Indeed the drug did show a 'favourable safety profile' with 'the most notable side effect' being 'a transient blue discoloration to the patients' skin' (Novacea, 2006a).

Despite the strong banoxantrone knowledge base, at the early stages of the project there was lack of molecular understanding of cells experiencing hypoxia. Indeed, the hypothesis that hypoxia was associated with tumour cells was based on practical evidence from radiologists not biomolecular evidence (interviewee H). This would be resolved with the proof of concept study published in 2008 (Albertella et al., 2008), however, this was late on in development of the drug.

Further evidence of the lack of knowledge available to support the development of banoxantrone, relates to the knowledge base in its indication. In the primary indication for which banoxantrone was being developed, glioblastoma, only 5,201<sup>117</sup> articles were published in the years preceding trials (up to and including 2000). This indicates a relatively sparse knowledge base, when compared with, for instance, the knowledge base accumulated during the same period for AML (25,139), and, although less pronounced, the knowledge base surrounding renal cell carcinoma which stood at 6,794.

This evidence indicates that there was a strong knowledge base for the development of banoxantrone, however, this was problematic due to the lack of molecular understanding of the drug mechanism until late on in drug development. Banoxantrone is categorised as having non-membership into the set extensive and accumulated knowledge base.

#### **7.4.4 Market Demand (QCA score = 0)**

Despite Pharmaprojects reporting the banoxantrone primary indication as brain cancer trials were undertaken in a variety of tumour types. The first, funded by BTG and

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<sup>117</sup> This figure was obtained using the Medical Subject Heading (MeSH) term 'Glioblastoma' as a search term in PubMed.

organised by Cancer Research Campaign (CRC) (part of Cancer Research UK) involved 22 patients suffering from oesophageal cancer (Steward et al., 2007, interviewee H). Subsequent trials tested the drug in advanced solid malignancies, lymphomas, ALL and brain cancer (Albertella et al., 2008, Papadopoulos et al., 2008, Benghiat et al., 2004, Sarantopoulos et al., 2006, Furman et al., 2006, Novacea, 2006b, Novacea, 2007b). The large market expectation of banoxantrone stemmed from the hypoxic characteristic of a 'large majority' of tumours (Novacea, 2006b) contributing to the 'significant potential' in a 'broad range of potential indications' (Novacea, 2003).

However, this was countered due to the need for banoxantrone to be used to enhance the effects of radiation (Novacea, 2003, interviewee H). Although hypoxic cells are found in a range of tumour types, within tumours only a portion of cells are hypoxic and other approaches are required to treat the non-hypoxic cells (McKeown et al., 2007).

In terms of competition, brain tumours were known to be a particular area of unmet clinical need, as highlighted by Novacea in their 2006 annual report, where glioblastoma is described as 'aggressive' with a 'relatively small patient population and [a] lack of effective therapies' (Novacea, 2006a). Indeed, this unmet need was one of the motivations, alongside the positive phase I results, that contributed towards the Novacea strategy to accelerate drug development as a first line therapy in glioblastoma. However, with the approval of the carmustine implant and temozolomide the glioblastoma market became more competitive (ibid).

Despite the focus on glioblastoma Novacea continued to emphasise the broad utility of banoxantrone. For instance, in 2007 John Walker, chairman and CEO states:

"the extensive pre-clinical and clinical data to date gives us confidence in the significant opportunity AQ4N [banoxantrone] presents as an anti-cancer agent in multiple tumor types and haematological malignancies" (Novacea, 2007a).

External observers were not so optimistic for the market potential of banoxantrone. For instance, Evolution Securities, the investment bank, predicted that the drug could generate sales of \$250m (Hume, 2005). This shows that, despite the large potential of banoxantrone in its application to a variety of tumours, potential sales indicated low expectations of the product.

However, this should be considered in the context of differing levels of revenues expected depending on the organisational context of the firm. Banoxantrone was initially developed by small companies, KuDOS and Novacea, who may have accepted smaller revenues, however, ultimately AZ discontinued the project. It is not unreasonable to

assume that one of the reasons for the lack of AZ interest in the project stemmed from the lack of worldwide rights to the project, as North American rights were sold to Novacea three years previously (see Table 27) (interviewee H).

This summary of the market issues surrounding banoxantrone demonstrate its broad applicability in cancer indications. However, the necessity for it to be used in combination with radiation limited the market the drug could demand and predicted sales were small. This justifies the non-membership into the set high market demand, and therefore the QCA score '0'.

#### **7.4.5 Stakeholder Perspectives (QCA score = 0)**

Banoxantrone was developed in the context of high expectations from the scientists involved, as highlighted above. In addition, media reports also exemplify this with the project described as 'potentially a major breakthrough' by the scientists involved (McIntyre, 2001, Erwin, 2001). In addition Novacea report 'significant potential' for the drug (Novacea, 2006a), and 'experts' label the drug 'one of the most important breakthroughs in recent years', (Gould, 2001). Other observers describe the drug as 'revolutionary' (Irish News, 2002, McCavana, 2002) and 'one to keep an eye on in the future' (Burke, 2005).

Additional expectations from the companies responsible for drug development are evidenced in their actions. At BTG this was exemplified by the unusual decision by BTG to fund the phase I trial (unusual because BTG did not frequently invest in early stage projects). Indeed in this thesis, despite the frequent involvement of BTG in projects that stemmed from academic research, in Campath, plevitrexed and Prolarix, there is no other evidence, with the exception of banoxantrone, of BTG funding clinical trials<sup>118</sup>.

At Novacea John Curd (Novacea Chief Medical Officer at the time) considered banoxantrone a 'breakthrough drug', believing in the mechanism so strongly that he also championed another bio-reductive agent, currently in phase III trials (interviewee H). Furthermore, even when Novacea began to step back their banoxantrone development programme, they still hoped to reinitiate the ALL study in the future (Cancer Drug News, 2008). Furthermore, high expectations were projected recently, in retrospect:

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<sup>118</sup> Upon investigation of the funders mentioned in the acknowledgement sections of clinical trial publications.

'banoxantrone, showed promise but work dwindled when owner Novacea was brought down by other clinical failures in 2008' (AmyB, 2012).

However, a patient and clinician perspective of banoxantrone centred on the notable side effect of the drug, a blue discolouration of patients' skin (Novacea, 2006a). Despite this being the only significant side effect (interviewee H) and that patients did not show direct reluctance, clinicians were apprehensive of this (email correspondence Y).

This evidence indicates that a broad range of observers, as well as those involved in the development of the drug itself, had positive expectations of the potential for the project. However, the issue around the blue colouration side effect was a negative stakeholder view in a critical constituency, namely clinicians. Therefore, banoxantrone cannot be classified as a member of the set positive stakeholder perspectives and scores '0' in the QCA.

#### **7.4.6 Organisational environment (QCA score = 0)**

BTG's involvement in drug development at this time was to aid the transfer of technology from academia to industry for commercialisation. In banoxantrone BTG became involved in the early stages and helped fund preclinical work, and a phase I trial. This support was in conjunction with funding from Ulster University and CRC. Subsequent to this KuDOS, a small UK therapeutics firm, licensed the project in 2002.

KuDOS, a spinout from Cambridge University, was founded in 1998 'to discover and commercialise novel drugs that target exciting new developments in DNA repair for the treatment of cancer and other diseases' (KuDOS Pharmaceuticals, 1999). With this cancer focus, the banoxantrone license was synergistic for KuDOS. KuDOS was motivated to take on the license to fill a gap in their pipeline by providing them with their first clinical stage product (email correspondence Y).

In May 1999 KuDOS received their first financing from venture capitalists amounting to £5m (KuDOS Pharmaceuticals, 1999). In 2002, the same year as the banoxantrone license, KuDOS received additional funding of £29.5m (KuDOS Pharmaceuticals, 2002). At this time the KuDOS pipeline also included PaTrin-2, a cancer therapeutic to enhance the efficacy of DNA-alkylating cytotoxins, licensed from Cancer Research Technology (CRT) late in 2002 (ibid). This supports the fit of banoxantrone in the KuDOS pipeline.

In 2003 another licensing agreement is taken out with Novacea, for North American rights to develop and commercialise banoxantrone (KuDOS Pharmaceuticals, 2003). Novacea was a small private company developing drugs for unmet needs in oncology and haematological conditions (Novacea, 2003). In 2003 Novacea had one additional



anticancer drug in late stage trials for advanced prostate and non-small cell lung cancer (ibid).

Novacea were committed to the development of banoxantrone, so when KuDOS was acquired by AZ in 2006, Novacea negotiated with AZ to acquire banoxantrone worldwide development and commercialisation rights (Novacea, 2007a). Due to the lack of North American rights to banoxantrone, the drug did not hold sufficient value for AZ (interviewee H) and so worldwide rights were transferred to Novacea. In addition, banoxantrone was not central to motivating the AZ, where KuDOS's oral poly-ADP-ribose polymerase (PARP) inhibitors and platform technology were the reason for acquisition (KuDOS Pharmaceuticals, 2005).

Little evidence of the interactions between KuDOS and Novacea has been identified, throughout the licensing agreements. However, Novacea did have particular interest in the discovery and development work that had preceded their license (interviewee H). This enthusiasm, for the science behind the project, is exemplified in the proof-of-concept trial undertaken at Novacea (Albertella et al., 2008) and the three presentations they announced at the 2005 American Association for Cancer Research Meeting (Novacea, 2005a).

Banoxantrone was described as representing 'a promising product opportunity for Novacea', and one that 'leverages [Novacea's] existing expertise in oncology and haematology and fits strategically with our focus on therapies that address unmet needs in cancer' (Novacea, 2005b). In this trans-Atlantic licensing agreement, it may have been difficult to continue a relationship between the researchers in the UK, who were previously involved in early stage discovery, development and trials, and the new USA researchers. Furthermore, in the UK, banoxantrone did benefit from having at least two project key individuals, Patterson and McKeown which may have contributed towards its early success. In addition, during KuDOS phase I trials, Professor Chris Twelves may have played a role in championing the project (interviewee H).

Novacea announced in 2006 that they would focus their resources on the development of their two anti-cancer leads, including banoxantrone. In addition, at this time they gained the worldwide rights to the project from AZ (Novacea, 2006c). However, in the subsequent years the firm suffered failure of their other phase III cancer drug (Market Wire, 2008), and were left with only banoxantrone in their pipeline. Despite having sufficient funds in the bank to continue development Novacea merged with Transcept who returned the banoxantrone license to BTG (Novacea, 2009, interviewee H).

This chronology of firms through which the development of banoxantrone passed exemplifies that, although initial development was smooth, the difficult environment surrounding small firms was ultimately the reason for project termination. Although banoxantrone was central to KuDOS's strategy, financial difficulties forced the firm to out-license North American rights to the project. When AZ acquired KuDOS they did not show interest in the drug. This may not have been terminal for the drug as Novacea remained enthusiastic, however when they suffered pipeline issues the difficult organisational environment led to project termination. This justifies the QCA score '0' indicating non-membership into the set supportive organisational environment.

#### **7.4.7 Banoxantrone Conclusion**

The early years of banoxantrone were positive and smooth. Initially market demand potential of banoxantrone were positive, with a broad set of indications the drug explored. However, the need to combine the drug with radiotherapy or conventional chemotherapeutics, implied a decline in its expected market demand and media reports a low level of potential peak sales.

The organisational environment of banoxantrone development and the involvement of small companies led to financial difficulties, resulting in the division of the worldwide rights. This diminished the attractiveness of the project to AZ when they took on responsibility for development. In addition, pipeline pressures, particularly while at Novacea, led to the eventual termination of the drug. Furthermore, the blue discolouration of patients treated with the drug led to negative users' perspectives, contributing to project discontinuation. Another aspect explored here that contributed towards the discontinuation of the development of banoxantrone is the lack of molecular understanding of the drug's mechanism of action, with development being based on practical/experiential knowledge until 2008.

The 'downers' mentioned here accumulated throughout drug development, instigating project drag, which surfaced when the protected space surrounding the project is broken down, upon the Novacea merger with Transcept.

### **7.5 TransMID – Complex History of Transactions**

In a similar pattern to banoxantrone, the case history of TransMID demonstrates a complex web of firms responsible for progressing development, in collaboration with the NINDS at NIH. This contributed towards a lengthy and prolonged process implying potential appropriability issues.

In addition, these transactions led to changing priorities, business models and strategies in the firms developing TransMID. For instance, when development shifted to the UK, from the USA in the early 2000s, in-licensed by KS Biomedix, the motivation came from a risk-mitigation strategy. However, although transactions surrounding the project occurred, in contrast to banoxantrone, it was only the management responsibility and not the research group that changed. This implies that, although turbulent, the knowledge accumulation surrounding the project is likely to have been consistent.

However, KS Biomedix and Xenova, ran into financial difficulties and could not support the expensive late stage TransMID. This led to the eventual acquisition of Xenova by Celtic who concluded insufficient commercial viability of TransMID. In a similar pattern to that seen in the development of banoxantrone, TransMID exemplifies the impact that vulnerabilities to the external environment can have on smaller firms.

As was the case in banoxantrone, these issues contributed towards the accumulation of project drag through TransMID's development. However, due to the action of the protected space surrounding the project, particularly while at KS Biomedix and Xenova, these issues lie latent. This breaks down when the project is taken on by Celtic whereby new evaluation criteria are implemented leading to project termination.

#### **7.5.1 Interview sources**

Two interviews were carried out to inform this case history, herein referred to as interviewee D and interviewee E.

#### **7.5.2 Introduction**

TransMID (ZR-311, CRM107, KSB-311) is an immunotoxin comprised of transferrin linked to the diphtheria toxin, developed to treat glioblastoma multiforme patients. The project stems from a discovery at the National Institutes of Health (NIH) (USA), and was developed by a series of pharmaceutical and biotechnology companies. Development of the drug was discontinued in 2007, reportedly for economic reasons.

<b>1989</b>	First immunotoxin (anti-CD25 single chain Fv and <i>Pseudomonas exotoxin</i> ) produced
<b>1994</b>	Sterling Winthrop licensed TransMID to Nycomed
<b>1996</b>	Carmustine implant approved as adjuvant to surgery in glioma patients
<b>1997</b>	Nycomed acquired Amersham; First trial results reported by NINDS (NIH)
<b>1999</b>	Approval of temozolomide (competitor) for recurrent glioblastoma
<b>2000</b>	Nycomed Amersham out-license TransMID to Avicenna; Phase II trial
<b>2001</b>	Avicenna acquired by KS Biomedix; NICE approval of competitor temozolomide; KS Biomedix receive fast track and orphan drug status for TransMID
<b>2003</b>	KS Biomedix acquired by Xenova
<b>2004</b>	TransMID Phase III trial initiated by Xenova
<b>2005</b>	Xenova acquired by Celtic
<b>2007</b>	Celtic discontinue development of TransMID

**Table 28 Key events in development of TransMID**

### 7.5.3 Knowledge base (QCA score = 0)

The research contributing to TransMID development began at the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) (part of the NIH, USA). TransMID is an immunotoxin comprised of a receptor targeting molecule conjugated to a toxin.

In TransMID, work on the receptor targeting molecule began the 1950s, when publications appear mentioning transferrin and its function as a glycoprotein responsible for controlling the level of iron in biological fluids (Laurell, 1951). The established nature of the knowledge surrounding the target, transferrin<sup>119</sup> is demonstrated in the number of associated articles found, amounting to 14,352.

However, this work was picked up by Ian Trowbridge at the Salk Institute for Biological Studies (California), who in 1981 reported a renewed interest in transferrin, and associated antibodies, stemming from the new mab technique developed by Kohler and Milstein in the 1970s (Trowbridge and Domingo, 1981). This research resulted in the discovery of an antibody to bind to the transferrin receptor on tumour cells. This was further developed whereby the transferrin antibody was conjugated to both the ricin and diphtheria toxins showing anti-tumour activity (ibid).

It was the NINDS that demonstrated that transferrin (the antibody) could be selective for central nervous system and brain tumours (interviewee D). However, the delivery of the

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<sup>119</sup> Search term used: (transferrin) AND ("1900/01/01"[Date - Publication] : "1995/31/12"[Date - Publication])

product into the brain was problematic, whereby the blood-brain barrier is a common issue in administering large molecules, such as antibodies (interviewee D). This was resolved using a delivery technology called intratumoural convection-enhanced delivery (CED) infusion that pumped the molecule into the tumour (Bobo et al., 1994, Weaver and Laske, 2003). However, this delivery method, and the placement of the pump was novel and difficult (interviewee E), requiring the accumulated tacit knowledge of the physicians involved.

Preclinical studies showed efficacy and safety in tumour models. In response, a phase I trial was designed as a single centre, dose-escalating single arm phase I trial and carried out at the NIH (Weaver and Laske, 2003, Laske et al., 1997). 18 adult patients were treated, nine showing partial response, defined by  $\geq 50\%$  decrease in enhancing volume of the treated tumour, and two showing complete response, defined as disappearance of all solid areas of enhancement of the tumour, with no severe neurologic or systemic toxicity (Weaver and Laske, 2003).

In 2000 a multicentre phase II was initiated involving 44 patients (Weaver and Laske, 2003). Of the 34 patients that were evaluable for tumour response 5 complete responses and 7 partial responses were found (responses in 35% of patients) (ibid). These results validated the Phase I studies and justified the use of TransMID as a glioma drug (ibid). Phase II results were presented in October 2002 (KS Biomedix Holdings PLC, 2002e), however, it took until 2004 for the phase III trial design to be approved and initiated. Here, the KS Biomedix design was previously, however, when acquired by Xenova the design was adapted requiring further approval (Xenova Group plc, 2004a). The trial was set up to recruit 323 patients (Xenova Group plc, 2004c), however enrolment was limited by strict eligibility criteria, and by May 2006 only 104 patients had been enrolled across 56 sites worldwide (Vrazo, 2006).

So far this section has demonstrated the problematic discovery stages of TransMID where high levels of uncertainty and problem solving were required, undertaken by an established team of researchers who had expertise in the area of immunotoxins (interviewee D). This implies that the knowledge development around receptor-antibody-tumour interaction and delivery issues, was overcome quickly and the project entered trials (at the NIH/NINDS) facilitated by involvement from the investigators involved in discovery phases (interviewee D). This is important as it means that any issues arising in these trials requiring input from investigators can be resolved. However, in later stages relationships broke down, and there was little interaction between later licensees, such as KS Biomedix, and the NINDS researchers (interviewee E).

Despite these difficulties the disease knowledge base contributing towards TransMID development publications mentioning the primary indication is quantified as high, where 22,319<sup>120</sup> articles were found mentioning glioma in the years preceding trials<sup>121</sup>.

TransMID research began in the 1960s, with the transferrin target found, in the 1980s, to display tumour overexpression. Transferrin (the antibody targeting the transferring receptor) was conjugated to the diphtheria toxin killing tumour cells when targeted by transferrin. This was a relatively new approach implying a high level of uncertainty and issues at early stages of development, with the first immunotoxin only being developed in 1989, and gemtuzumab synthesised in the early 1990s. Despite the interactions between researchers in the early stages of drug research, this relationship was lost later on. In addition, extensive tacit knowledge was required for administration of the drug, implying the importance of knowledge transfer. This justifies the non-membership of TransMID in this set, extensive and accumulated knowledge base.

#### **7.5.4 Market demand (QCA score = 0)**

Despite a range preclinical investigations for TransMID glioma cells that showed the highest response (Weaver and Laske, 2003, Pharmaprojects). Patents for TransMID, taken out by NIH, covered cancers of the head, neck and central nervous system (Xenova Group plc, 2003a). Tumour specificity of TransMID was limited by the expression of Transferrin receptors on tumour cell surfaces. This limitation of the project implied a small population of patients who would make up the potential market for the drug.

In response to preclinical results, phase I and II studies were undertaken in brain tumour patients (Laske et al., 1997, Weaver and Laske, 2003). In 2002 KS Biomedix estimated brain cancer incidence in Europe as 20,000 per year, of which 50% have high-grade gliomas with a life expectancy of around six months (KS Biomedix Holdings PLC, 2002c). In 2001, the expected worldwide market for TransMID (including for the treatment of recurrent, inoperable high grade glioma and primary brain tumours) stood at \$600m annually (KS Biomedix Holdings PLC, 2001c), with the 'triad region' (typically North America, Western Europe and Japan) standing at an estimated \$210m - 'quite a small market but very focused' (The Wall Street Transcript, 2001).

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<sup>120</sup> This figure was obtained using the Medical Subject Heading (MeSH) term 'glioma' as a search term in PubMed.

<sup>121</sup> Up to and including 1995

However, KS Biomedix planned for trials to be expanded to paediatric newly diagnosed and metastatic brain cancer (The Wall Street Transcript, 2001, KS Biomedix Holdings PLC, 2003a). The potential for the drug in these expanded areas impacted the predicted market. For instance, KS Biomedix expect a market potential of US\$3.8bn annually, when including the additional indications (KS Biomedix Holdings PLC, 2001c).

Despite the small glioblastoma patient population it is characterised by severe unmet clinical need, where the prognosis of patients has not changed in the last 20 years (Weaver and Laske, 2003). It was part of the Xenova strategy to emphasise the unmet need of this indication. During the few years that Xenova was responsible for TransMID glioblastoma is described as an 'unmet need' (Sosei Co. Ltd, 2005), a 'type of brain cancer for patients with an otherwise poor prognosis' (QSV Biologics, 2004) and an area with 'limited therapeutic alternatives' (Xenova Group plc, 2004c). The perception of TransMID as fulfilling an unmet need implies its development is socially beneficial. In addition, a lack of competition in this therapeutics area implies a potential for high prices to be obtained for the approved product. However, this may have changed with the introduction of the carmustine implant in 1997 and temozolomide in 1999 which both became a standard of care for brain tumour patients in the early 2000s.

Due to the lengthy duration of the development of TransMID associated patents were nearing expiry. TransMID patents were filed in 1989 (Johnson et al., 1993), 1990 (Pastan et al., 2000), 1992 (Johnson and Youle, 1994) and 1994 (Johnson and Youle, 1998), implying expiry dates of the mid-2010s. When Celtic in-licensed the drug, in 2005, they needed to complete a phase III trial, usually taking an average of four years, (Abrantes-Metz et al., 2004). This implies that there would only have been five years remaining of patent protection when an application for approval was submitted, although the potential to apply for a supplementary protection certificate could counteract this effect.

In summary, TransMID's potential market size, despite showing a large amount of variation in estimates, is projected to be small but potentially lucrative due to the unmet clinical need and the lack of competition of brain cancers. However, competition did appear in the late 1990s and early 2000s. Furthermore, with patent protection for the drug waning, concerns for appropriability of returns from the drug would have been justified (although not mentioned specifically). These factors contribute towards the characterisation of TransMID as a non-member in the set high market demand.

### 7.5.5 Stakeholder Perspectives (QCA score = 0)

Scientific expectations of the project benefitted from the novelty of immunotoxins. Indeed, when KS Biomedix acquired Avicenna KS Biomedix had high hopes for the project, largely based on anecdotes from trials, reporting miraculous recoveries. The company acquired the drug both to broaden their oncology portfolio and due to their belief that the drug would change the lives of brain cancer patients (interviewee E). Furthermore, the potential that Xenova saw for TransMID development also motivated the KS Biomedix, (KS Biomedix Holdings PLC, 2003c, Xenova Group plc, 2003b, interviewee E). This indicates the support felt from industry partners involved in TransMID development.

In the media high expectations for the drug are observed. In 1997 there are several articles describing the project positively, including descriptions of TransMID as having 'shown promise' and providing 'hope in fight against brain cancer' (Stobbe, 1997). However, later in development the media are not hopeful for the firms responsible for TransMID. One article quotes an analyst from the investment bank, ING, in saying

'KSB has long been trying to raise funds, and it has failed. The best deal they could get for their shareholders was at a discount to the current share price. On paper, TransMID is an interesting compound, two or three years away from launch. Someone could have snapped it up, but they haven't, and in the end the only one they could sell to was a company [Xenova] which is itself in dire straits' (Foley, 2003)

However, the following year demonstrates optimism for the drug due to the approval of the protocol for, and planned initiation of, the phase III, driving Xenova share prices up (Hasell, 2004). This was described as follows in The Times: 'it was this excitement [of the prospect of the initiation of the phase III trial] surrounding that product [TransMID] which drove yesterday's rally' (ibid).

The patients and clinician perspective of the drug is influenced by the availability of treatments and their administration. Prior to 2000 there were little treatment options for brain tumours. However, this changed in the late 1990s/early 2000s when the carmustine implant and temozolomide were approved by regulatory agencies and recommended by the NICE in the UK.

In addition to the emergence of competitors in the brain tumour indication, TransMID also have suffered from a negative perception by clinicians and patients due to the administration of the drug. The CED infusion administration route was seen as an invasive procedure as the drug was administered directly into the brain. When compared



to an orally administered drug, such as the competing temozolomide, the patients and clinician perspective of the drug, by, benefitted from the ease of oral administration.

The expectations of stakeholders during the development of TransMID indicate a complex mix of perceptions. Negative, from industrial partners, patients and clinicians, and positive, from scientific investigators and firms in-licensing the drug, due to the belief of the potential for patient benefit. Furthermore, the invasive nature of the drug is likely to have contributed towards the problematic perspectives felt by users. This evidence implies that membership into the set positive stakeholder perspectives is not conclusive, thereby justifying the QCA score of '0'.

#### **7.5.6 Organisational environment (QCA score = 0)**

The license(s) for TransMID (CRM107) were transferred through a complex network of firms throughout the 1990s and 2000s. This is had detrimental impact on the development of the project (Vrazo, 2006).

When TransMID was discovered NINDS investigators were working with scientists at Cetus Corporation, one of the first US biotechnology companies, who had licensed the Transferrin antibody technology from Ian Trowbridge (Johnson et al., 1996, interviewee D). However, when Cetus Corporation were acquired by Chiron Corporation in 1991 (Fore et al., 2006), researchers needed another partner to produce the antibody under good manufacturing practices (interviewee D). Initially Nycomed, fulfilled this role, with Avicenna taking on manufacturing later.

Firstly, the project passed to Nycomed through their acquisition of a division of Sterling Winthrop, a by-product of the Sanofi acquisition of Sterling Winthrop (The Globe and Mail, 1994). In this it was observed that Sanofi always had the intention of divesting part of the Sterling Winthrop business amounting to the activities 'that it deemed as non-strategic' (ibid), indicating that TransMID was not strategic in Sterling Winthrop or Sanofi.

Avicenna, a Canadian manufacturing start-up (1992), consulting for Nycomed (Medicenna Therapeutics INC., 2014), took on the manufacturing of TransMID, in 2000, as a result of Nycomed-Amersham deals (Medicenna Therapeutics INC., 2014, interviewee D). Prior to this, while the project was at Nycomed/Amersham<sup>122</sup> little progress was made to develop the project (interviewee E).

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<sup>122</sup> Nycomed and Amersham merged in 1997 but in 2000 Amersham decided to divest the Nycomed business.

Development of the drug and trials were undertaken at the NINDS (NIH) (Weaver and Laske, 2003, Bobo et al., 1994, interviewee D, Laske et al., 1997), with Nycomed having some involvement in trial design (interviewee D), however it wasn't until the license with Avicenna was initiated that the investigators at the NIH had a high level of involvement and communication with their industrial partners (interviewee D). This was integral to the phase II trial undertaking, however, when Avicenna was acquired by KS Biomedix, this relationship did not continue (interviewee D).

At the time of the KS Biomedix acquisition TransMID was Avicenna's lead candidate (AFX.com, 2001a). This acquisition of Avicenna, by KS Biomedix, was strategic, motivated by the desire to build an oncology portfolio (interviewee E). Furthermore, it provided KS Biomedix with a presence in North America (London Stock Exchange Aggregated Regulatory News Service, 2001). Despite the acquisition the production of TransMID remained in the same location, whereby KS Biomedix retained the Canadian Avicenna site (Zehr, 2001).

However, when the project passed to KS Biomedix, not only did responsibility for development pass to them, in the form of the need to initiate phase III trials with a lack of involvement from the NINDS team, but they also had to fund this R&D. In 1996, just 6 years after the company was founded, KS Biomedix floated on the Alternative Investment Market of the London Stock Exchange (KS Biomedix Holdings PLC, 1995).

When KS Biomedix took on TransMID they appreciated that it would be an expensive venture, and put together a strategy to raise sufficient funds for the phase III trial (interviewee E). This involved a stock-market financing round to raise the funds for the acquisition and trial (interviewee E). KS Biomedix demonstrated success in returning to the stock market to access additional funds. In just the previous year, managed to raise around £15m (KS Biomedix Holdings PLC, 2000). In addition from 1996 to 2001 the firm raised £26m in 5 years (The Wall Street Transcript, 2001). In 2001, the intention was to raise in the region of £30m (interviewee E) however, due to market conditions, and the fluctuation of the stock markets, only £16m was eventually raised (KS Biomedix Holdings PLC, 2001d).

This was a blow to the KS Biomedix strategy, particularly considering that during TransMID development the KS Biomedix pipeline included two lead inflammatory disease products in phase II trials, and TransMID entering phase III (AFX.com, 2001b). The advanced stages of these products meant that the company had a high burn rate (£4m, compared to £1.9m in the previous year) (ibid), amplifying the issues associated with disappointing stock-market placings, as discussed above. Furthermore, share prices fell

when one of the inflammatory disease products produced disappointing results in the phase II trial (Pharma Marketletter, 2001).

This was partially addressed due to a series of licensing agreements for the commercialisation of TransMID in 2002 (KS Biomedix Holdings PLC, 2002b, KS Biomedix Holdings PLC, 2002c). These licensing agreements allowed KS Biomedix to continue developing TransMID by beginning a phase II in paediatric brain cancer patients, receiving orphan drug status (in the USA and EU) and the potential for fast track approval from the FDA (KS Biomedix Holdings PLC, 2001c, KS Biomedix Holdings PLC, 2001a, KS Biomedix Holdings PLC, 2001b, KS Biomedix Holdings PLC, 2002e, KS Biomedix Holdings PLC, 2002d, KS Biomedix Holdings PLC, 2002a).

In addition, the company spent time negotiating with the FDA on the phase III trial design. However, when Xenova acquired KS Biomedix it was stated that the approval for the phase III study design was taking 'longer than originally envisaged' due to the introduction of the Special Protocol Assessment Committee at the FDA (KS Biomedix Holdings PLC, 2003b).

On the acquisition Xenova valued KS Biomedix at just £17m, including a consideration in relation to TransMID of £6.5m (Xenova Group plc, 2003c). TransMID was one of the main motivations for Xenova's acquisition of KS Biomedix, where the product became Xenova's lead compound, filling the pipeline gap arising from the disappointing Tariquidar results, a failed chemotherapy agent for non-small cell lung cancer (Xenova Group plc, 2003a). This indicates that Xenova did have cancer capabilities. The strategic value of TransMID to Xenova is demonstrated when it is described as their 'jewel in the crown' (Investors Chronicle, 2003).

Xenova went back to the FDA for approval of an amended phase III trial design involving two smaller sequential trials, as opposed to the previous larger one (Xenova Group plc, 2004a). This change was motivated by the projected study costs whereby the KS Biomedix protocol was expected to cost around £18m which was halved in Xenova's proposed trial (Investors Chronicle, 2003).

Despite Xenova rapidly receiving approval for the phase III study design, like KS Biomedix, they struggled to raise sufficient funds for the trial. In September 2004, in an effort to reduce turnover costs of the firms, Xenova sold its manufacturing facility (previously KS Avicenna) to QSV Biologics (for £2.9m), who took on TransMID manufacturing (Xenova Group plc, 2004b).

Furthermore, Xenova extended KS Biomedix's commercialisation licensing strategy, in April 2005 when PharmaEngine gained commercialisation rights for TransMID in China and South Korea (Xenova Group plc, 2005). However, these finance strategies were not sufficient, and the company was put up for sale and was acquired by Celtic Pharma in September 2005 (Celtic Pharmaceutical Holdings LP, 2005). Celtic's support for TransMID was short lived, and despite continuing with the phase III trial, in February 2007 it terminated development, for both technical and economic grounds:

'At the end of 2006, ahead of incurring significant planned expenditure in 2007, Celtic Pharma undertook a condition power analysis. The aim of this analysis was to evaluate, on the basis of the first one third of events, the probability of the TransMID treated patients achieving the study's targeted increase in survival at study end, as defined in the protocol. The completed analysis showed that it was extremely unlikely that TransMID would meet the trial criteria for efficacy. Accordingly, Celtic Pharma has decided to terminate the trial and further clinical development of TransMID on commercial grounds. The trial Data Monitoring Committee has independently recommended to Celtic Pharma and the Trial Steering Committee the trial be stopped on medical grounds.' (Celtic Pharmaceutical Holdings LP, 2007)

Due to the lack of publications indicating these clinical trial results, it is difficult to contextualise Celtic's claim, of discontinuing on medical grounds. However, it is not unreasonable to assume that in order to compete with competing brain cancer drugs, e.g. temozolomide, TransMID would have had to show improved efficacy, compared to standards treatment, which may not have been satisfied.

From an economic perspective when Celtic Pharma acquired Xenova their strategy as a private equity fund was to acquire late stage products and develop them to approval, whereby Xenova would become their drug development arm in the UK (Market Wire, 2005). This primary motivation of Celtic, of their investment strategy (Celtic Pharmaceutical Holdings LP, 2007), was central to their decision to discontinue TransMID development. This is in contrast to a bio-pharma firm, who may have been more concerned and committed to the scientific interest in the product.

The organisation environments that surrounded the development of the TransMID project may have had detrimental consequences for the drug. Firstly, the number of companies through which the project passed slowed development down. In addition, the difficult funding environment facing small biotechnology firms, particularly in the UK was also key to this story, whereby firms demonstrably could not financially support the project. These factors justify the non-membership of this case into the set supportive organisational environment (QCA score '0').

### **7.5.7 TransMID Conclusion**

The TransMID case history is complex and shrouded in organisational issues, mixed expectations and uncertainty over the novel therapeutic approach. These uncertainties that were seen in the initial phases of discovery and early development were overcome by problem solving and committed investigators in the uncertain technological area.

The novelty of this approach contributed to high expectations surrounding the project, however there were also reported of negative perspectives of the project. One of the major issues in the development of TransMID appears to be the complex arrangement of organisations that took on its development. These companies were also faced with their own environmental constraints, mainly around funding.

These issues contributed towards project drag, however, this was latent until the breakdown of the protected space upon the Celtic Pharma acquisition. This case presents the strongest evidence to show that the acquiring firm implemented a more objective evaluation procedure whereby issues were uncovered that previously were deemed conquerable.

## **7.6 Prolarix – Delays and Difficulties**

Prolarix (NQ02, Caricotamide and tretazicar), in a pattern reminiscent of TransMID, underwent notable delays during development, stemming from difficulties in regulatory requirements for trials. This contributed towards cash difficulties for the small firms involved, due to longer periods of high burn rate.

In the Prolarix these delays led to project drag and were central to motivating changes in the organisational environment surrounding the project, as the firms encountered funding difficulties had to be acquired. Furthermore, these organisational changes contributed towards knowledge transfer and accumulation issues, and in the absence of a key individual championing the project, these problems contributed to the termination of the project. In addition, the project suffered from the additional issues of small market potential and a lack of media/stakeholder coverage.

### **7.6.1 Interview sources**

No interviews could be undertaken to inform this case history.

### **7.6.2 Introduction**

Prolarix was primarily in development for the treatment of hepatocellular carcinoma (HCC) (liver cancer). The drug was made up of caricotamide (EP-0152R) and tretazicar (CB1954). The early stages of clinical development were undertaken at a small UK

biotechnology firm called Enact. When Enact was acquired by Protherics development of Prolarix continued. When BTG acquired Protherics it too continued development of Prolarix for a year, but then subsequently discontinued the project in 2009.

<b>1995</b>	ENACT (ENZACTA) founded
<b>2002</b>	Cancer Research UK sponsored Phase I trial for Prolarix agreed
<b>2003</b>	ENACT acquired by Protherics
<b>2004</b>	Prolarix enters Phase II
<b>2007</b>	Liver cancer competitor (sorafenib) introduced
<b>2008</b>	Prolarix Phase II initiated in liver cancer; Protherics acquired by BTG
<b>2009</b>	Prolarix discontinued by BTG

**Table 29 Key events in development of Prolarix**

### **7.6.3 Knowledge base (QCA score = 0)**

Prolarix is made up of caricotamide, a cosubstrate, and a prodrug tretazicar (CB1954). The mechanism of action of the drug uses the endogenous NQO2 enzyme, found to be latent in certain tumour cells but activated by caricotamide, which in turn converts tretazicar to a cytotoxin (Pharmaprojects(London Stock Exchange Aggregated Regulatory News Service, 2006b)).

The scientific background of Prolarix dates back to the 1950s when CB1954 was identified from a large series of aziridines, synthesised and investigated for tumour growth inhibition (Knox et al., 1993). CB1954 was found to have a high therapeutic index when tested on the Walker 256 carcinoma tumour model *in vivo* (ibid). Despite extensive studies and a trial in 1970 showing responses in rat tumour models, no effect was present in human tumours (ibid). In 1986 CB1954 was described as ‘a drug in search of a human tumour to treat’ (Workman et al., 1986, Knox et al., 1993, Newell et al., 2003).

The research pathway around CB1954 changed in 1993 when scientists began to understand the compound’s mechanism of action. Here CB1954 was found to be activated by the NQO2 enzyme in rat tumours, an enzyme that was found to be latent in human tumours (Knox et al., 1993, Knox et al., 2000). To activate the enzyme in human tumours three alternative strategies were suggested: 1) an analogue to CB1954 that could be reduced into a cytotoxic agent in tumour cells, 2) exploring pyridinium compounds that could enhance the CB1954 cytotoxicity, or 3) administering a CB1954 activating enzyme that could target human tumours by conjugating to an antibody (known as the Antibody-directed enzyme prodrug therapy (ADEPT) approach) (Knox et al., 1993).

It was the second of these approaches that was explored in the production of Prolarix. In 2000 Knox, a researcher from the Institute of Cancer Research, and colleagues published a paper that explored a number of pyridinium compounds to activate the NQO2 enzyme in tumour cells (Knox et al., 2000). This prodrug approach was less complex than the alternative ADEPT approach: 'it might be possible to use CB1954 directly for prodrug therapy of human tumours without the complications associated with macromolecular targeting systems required for GDEPT [gene-directed enzyme prodrug therapy] and ADEPT' (ibid). This prodrug system was a novel approach to the delivery of cancer therapeutics and was described as 'the first example of a latent enzyme-prodrug system switched on by synthetic co-substrate' (ibid).

Once a suitable co-substrate compound was identified (Knox et al., 2000) it was tested in preclinical animal models. Tretazicar and caricotamide (Prolarix as it was later known) was found to be particularly effective in liver samples, as well as colorectal and pancreatic tumour cells, due to the higher concentration of the activating enzyme NQO2 in these cells (Pharmaprojects).

In 2001 the compound was ready for trials (Enact Pharma, 2001), however due to a delay caused by changes to the regulatory environment, the project did not enter trials until 2005 (Protherics, 2005a). These changes were introduced under an EU Directive on clinical trials which set out that all trials should be undertaken under Good Clinical Practice and products in trials should be made to Good Manufacturing Practice (Newell et al., 2003). Furthermore, the previous exemption from obtaining a Clinical Trials Certificate for doctors and dentists conducting trials on their own patients, was also removed (ibid).

Phase I trials results were not published until 2010 when investigators reported that testing of the drug showed that the NQO2 enzyme was selectively activated by caricotamide in a trial involving 32 patients (Middleton et al., 2010). In addition, NQO2 activity was found to be higher in solid tumour cells than in normal cells, with the highest activity found in liver cancer tissue (ibid). Toxicity of patients in this study was low, with less than a quarter of patients showing grade 3 or 4 toxicity at the maximum tolerated dose (ibid). Therefore, this phase I trial provided 'sufficient proof of mechanism to warrant advance of this prodrug system into phase II efficacy trials for HCC patients' (ibid).

This phase II trial programme was planned for 2008 in HCC (Protherics, 2008a). In addition, there are also plans to begin a phase II programme to combine sorafenib with Prolarix and compare with sorafenib alone (ibid). However, in 2008 Protherics was acquired by BTG. Prolarix was not mentioned until November 2009 when phase IIa were

discontinued to allow BTG to seek a specialist oncology partner (British Technology Group, 2009c).

From the data available it is difficult to conclude the consistency of the Prolarix investigators, due to the lack of published material presenting trial results. In the article from 2010 there are researchers from BTG (ex-Enact employees), University of Oxford, Royal Marsden, UCL Cancer Institute, and CR-UK (Middleton et al., 2010). In addition, the 2000 discovery research publication lists authors from Enact, University of Bradford, ICR and Beckman Research Institute (California) (Knox et al., 2000). This implies that, despite the diversity of researchers investigating the drug, Enact employees had a high level of involvement in the process, collaborating with other researchers, with Knox appearing prominently in both articles (first author in one, second author in the other).

However, Prolarix scores high when considering the knowledge accumulated in the primary indication disease area. Here 24,506<sup>123</sup> articles were found mentioning HCC in all years preceding the initiation of trials<sup>124</sup>. However, no articles were found mentioning caricotamide AND (tretazicar OR CB1954)<sup>125</sup> prior to the year Prolarix entered clinical trials, and only 31 were found mentioning NQO2<sup>126</sup> during this period.

From the evidence presented it is clear that despite the established and promising research pathway forming the basis for Prolarix, the phase I trials were limited, particularly in those that were published (with only one publication mentioning trials (Middleton et al., 2010)) and, despite conveying promising results, phase II results were never obtained to confirm these. These factors justify the QCA score of 0.

#### **7.6.4 Market demand (QCA score = 0)**

From early development of Prolarix the drug was specifically aimed at liver cancer. This resulted from preclinical studies findings investigating Prolarix in human tumour xenografts showing increased activity of the NQO2 enzyme in liver samples In addition high activity was also found in colorectal and pancreatic tumours (Pharmaprojects). This

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<sup>123</sup> This figure was obtained using the Medical Subject Heading (MeSH) term 'Carcinoma, Renal Cell' as a search term in PubMed.

<sup>124</sup> Up to and including 2004

<sup>125</sup> Search term used: ((caricotamide AND (CB1954 OR tretazicar))) AND ("1900/01/01"[Date - Publication] : "2002/31/12"[Date - Publication])

<sup>126</sup> Search term used: (NQo2) AND ("1900/01/01"[Date - Publication] : "2002/31/12"[Date - Publication])



informed a phase I trial strategy which was to realise potential in liver, colorectal and pancreatic cancer patients (Enact Pharma, 2001).

After a long delay caused by regulatory issues, in 2005 Protherics stated that the drug was in a phase I study in patients with solid tumours in general (Protherics, 2005a). However, in the following year the Protherics had plans to pursue development in HCC despite the phase I that was underway at the time (Protherics, 2006).

In 2008 Protherics further highlights the wider market potential for Prolarix, including ovarian cancer and melanoma (Protherics, 2008a). These expectations indicate that despite the potential for the drug to be specified to liver cancer, and the immediate strategy to progress with this indication, there was also potential to widen the therapeutic applicability at a later date.

In addition Protherics, on acquisition of Enact in 2003, quantify their expectations of market size when they claim that the worldwide market for an effective HCC treatment could reach an estimated £2.8bn per year, due to the area being one of high unmet clinical need (Protherics, 2003a). This implies that despite the relatively low numbers of people affected by the cancer, mortality figures were high, quoted to be 120,000 for liver, colorectal and pancreatic tumour patients per year in the USA and UK combined (Enact Pharma, 2001). This represents a high proportion, where a total of 563,700 cancer deaths were expected in the US in 2004 (Jemal et al., 2004). For the liver cancer indication solely the Protherics Chief Executive, in 2004, stated that Prolarix could achieve sales of \$250m (Clay, 2006).

HCC remains an area of unmet clinical need, particularly in the UK, despite the development and approval for the kinase inhibitor sorafenib which was approved in 2007 for HCC, due to the lack of recommendation of the drug from NICE (National Cancer Institute, 2013, National Institute for Health and Care Excellence (NICE), 2010). This decision by NICE may have impacted the development of Prolarix, providing a level of comparative efficacy, safety and cost-effectiveness, and thereby setting the bar higher for additional clinical candidates.

Despite the long development times of Prolarix, due to delays in getting approval for trials (as will be discussed later in this discussion), the patents associated with the drug were not filed until 1998 (Burke and Knox, 2005) and 2002 (Burke and Knox, 2006), and therefore would not be expected to expire until 2022. This indicates that imminent patent expiry was not a factor in contributing towards the drugs termination, based on the

average phase II and III duration being 6.5 years (Abrantes-Metz et al., 2004), with the Prolarix phase II being initiated in 2004.

This section shows that despite Prolarix showing a range of potential indications, HCC, the primary cancer indication, had a competing product introduced in the late stages of Prolarix development (during phase II). Furthermore, due to the lack of orphan drug designation at the time of development the drug was not subject to the benefits of this or any other regulatory policy. These factors, taken on balance indicate that the drug cannot be classified as a member of the set high market demand, thereby the QCA score of 0 has been allocated.

#### **7.6.5 Stakeholder Perspectives (QCA score = 0)**

Prolarix received little coverage in the national newspapers. There are two mentions of the drug in mainstream, i.e. non-specialist, newspapers that report Prolarix positively, for instance describing Protherics of having ‘high hopes’ for the project (Manchester Evening News, 2004) or stating that the project’s results ‘appear favourable’ (Freeman, 2005), however these are in local newspapers and therefore not as influential as comments made in national or international media. The high expectations of Prolarix as projected from Protherics are further highlighted in interim results in both 2005 (Protherics, 2005b) and 2007 (Protherics, 2007b).

This lack of press coverage is perhaps surprising considering the support in trials and early stage discovery and development coming from CR-UK. CR-UK is mentioned in line with supporting and organising the trial however there is no specific coverage coming from the charity claiming support for the project. This may be an indication that Cancer Research UK may not have had particularly high interest in the development of Prolarix. This may stem from the overshadowing of Prolarix by the interest in a sister molecule that was developed (again by Enact and Protherics), also utilising the CB1954 but being applying using gene therapy in prostate cancer, which received a high level of interest in 2001 from major newspapers (Charter, 2001, Connor, 2001, Hall, 2001).

A lack of media coverage, which is particularly surprising due to the involvement of CR-UK in the development of Prolarix, is the main justification for the QCA score of 0, non-membership into the set positive stakeholder perspective.

#### **7.6.6 Organisational environment (QCA score = 0)**

Most of the initial work on the CB1954 compound and the identification of a suitable co-substrate for the prodrug application of the project was carried out by researchers at the ICR, led by Richard Knox (Knox et al., 1988a, Knox et al., 1993, Knox et al., 1988b, Knox

et al., 1991, Roberts et al., 1986). A collaboration that continued throughout the development of the project.

Enact Pharma (previously called Enzacta) took on Prolarix development as they were founded on the basis of the ADEPT technology which formed an alternative possibility for the delivery of CB1954 to treat cancer patients. The ADEPT technology was proposed in 1987 (Bagshawe, 1987), investigated by a group of scientists who were later the Scientific Directors of Enact (Enzacta Group plc, 1999). In 1995 a company called AEPACT was established to develop the ADEPT technology (ibid). In 1998 AEPACT was acquired by Prodrug Pharma who subsequently changed their name to ENZACTA (ibid). This complex pathway to the foundation of Enact (Enzacta) was focused on the development of the ADEPT technology, therefore, establishing Prolarix as lower priority. However, funding from Cancer Research UK enabled the firm to progress the project.

The commitment from CR-UK continued throughout preclinical development and into phase I, which was expected to be run by Professor David Kerr, clinical head of the CRC Institute for Cancer Studies, University of Birmingham (Enact Pharma, 2001). At this time in line with the aforementioned EU Directive on clinical trials, manufacturing regulations changed meaning that the materials used in early phase trials needed to comply with Good Manufacturing Practice regulations, therefore implying a major set-back for Prolarix development. This was due to the need for CR-UK to reformulate the drug and work with the formulation contractor to do so (Enact Pharma, 2002). Despite this regulation being introduced in 2001, the approval from the Medicines and Healthcare products Regulatory Agency in the UK for the improved formulation was not received until 2006 (London Stock Exchange Aggregated Regulatory News Service, 2006b).

By the time the trial had begun, in 2004/05, Enact had, in 2003, been acquired by Protherics (Protherics, 2003c). The motivation for the acquisition was primarily the Enact lead compound, Voraxaze, with secondary attention on the continued development of Prolarix (ibid). At this stage the motivation from the Enact perspective is said to be linked to a lack of funds: 'without further funding in the short term, the Company [Enact] would need to reduce its operational activities significantly and would be unable to fund the development of its core drug development programmes' (Protherics, 2003c:5).

Once Protherics had acquired ENACT, coinciding with Prolarix's entrance into phase I trials, they stated their intention to out-license the product to a marketing partner within two years (Protherics, 2003b). This strategy changes, however, as demonstrated in the 2006 annual report which states "Protherics intends to fully develop and undertake the sales and marketing of Prolarix in the US and EU" (Protherics, 2006). Despite this,

Protherics make little progress in the development of Prolarix which remained in phase I with 23 patients treated in 2007 (Protherics, 2007a).

In 2008, however, just after the announcement of the initiation of the phase II study for Prolarix (Protherics, 2008b) in HCC patients, BTG acquired Protherics (British Technology Group, 2008). BTG's initial intention was to develop Prolarix through phase II trials and then out-license (British Technology Group, 2009b). However, in the 2009 annual report BTG stopped the phase II study to 'seek a specialist oncology partner', which was unsuccessful (British Technology Group, 2009a).

The firm dynamics, which surrounded the development of Prolarix throughout two acquisitions involving a shortfall of financing imply an unsupportive environment for drug development. These issues may have had a detrimental impact on the development of the project. In addition, the delays due to changes in manufacturing legislation for trials came at an integral time in the projects history. This is taken to contribute towards the non-membership of Prolarix into the set supportive organisational environment and justifies the score 0.

#### **7.6.7 Prolarix Conclusion**

Prolarix did have the potential to be applied to a range of indication types, however this, in addition to the extensive and supportive discovery-related science, were the only straightforward aspects of the drug's development. The clinical trials, expectations surrounding the development of the drug and the complex organisational environment contributed to the decision to discontinue Prolarix development. These aspects are linked. Funding issues, and delays contributed towards a lack of clinical data, which did not support the justification for continuing development for the project by BTG. In addition, if the drug had been subjected to the media coverage that has been found to be associated with other charity-developed drug projects (see temozolomide) it may have been a more attractive licensing prospect for BTG and, later another industrial partner.

### **7.7 CAT-3888 – Overshadowed by a Follow-on**

The development of CAT3888 (synonyms: BL-22, GCR-3888), a recombinant immunotoxin, suffered from 5 issues that contributed towards its eventual termination: 1) low market potential, 2) novel and uncertain market, 3) novel and uncertain knowledge base, and 4) differences in risk-associated thresholds between large and small firms upon portfolio evaluation.

The novelty of the project contributed towards initial interest and excitement, and, as it was being developed, first by academic researchers and then by a small firm (CAT), the

desire for proof of concept may have overcome the issues associated with novelty and uncertainty, as was the case for gemtuzumab.

Furthermore, with the project being led by a research team, and later by small firms, the low market potential would be more acceptable than in larger firms. However, taking the small market opportunity, in the context of an emerging follow-on product that was comparable but more efficacious in a broader range of indications, it is perhaps not surprising that CAT3888 was discontinued upon acquisition of CAT by AZ. Here we observe that rather than project drag accumulating around the project leading to a loss of momentum, it is the gaining of momentum by another similar project that is the key motivator. Furthermore, we observe that where evaluation criteria were suspended or had different thresholds while the project was at CAT, the action of the breakdown of the protected space when AZ acquired, contributed towards a re-evaluation and subsequent discontinuation of CAT3888, in favour of CAT8015.

#### 7.7.1 Interview sources

An interview was carried out with one individual involved in the development of CAT3888, interviewee G.

#### 7.7.2 Introduction

CAT-3888 is a recombinant immunotoxin, comprised of a disulfide linked Fv antibody fragment conjugated to *Pseudomonas* exotoxin PE38. The drug targets the CD22 antigen on tumour cells, and so, despite being developed primarily for the treatment of hairy cell leukaemia (HCL), also showed some efficacy against other B-cell malignancies. Development of CAT-3888 was initiated at the National Cancer Institute (NCI) in the USA (part of the National Institute of Health), licensed to Genencor, and later in-licensed by the British biotechnology company, Cambridge Antibody Technology (CAT).

<b>1989</b>	First immunotoxin (anti-CD25 single chain Fv and <i>Pseudomonas</i> exotoxin) produced
<b>1999</b>	CAT3888 Phase I trials begin
<b>2001</b>	Results from Phase I presented
<b>2003</b>	CAT3888 Phase II trial begins
<b>2004</b>	NCI signs CRADA with Genencor
<b>2005</b>	NCI CRADA passed to CAT with license
<b>2006</b>	CAT acquired by AZ
<b>2007</b>	AZ discontinues development of CAT3888

**Table 30 Key events in development of CAT3888**

### 7.7.3 Knowledge base (QCA score = 1)

The knowledge providing the basis for CAT3888 can be traced to work undertaken in Ira Pastan's lab at the NCI in the 1970s and 1980s (Pastan, 2003). During the development of the drug, despite the disruptions caused by varying licensing agreements and acquisitions, the project did benefit from a relatively consistent research team throughout, facilitated by the cooperative research and development agreement (CRADA), signed initially between NCI and Genencor, and passing to CAT.

Pastan's NCI lab work on immunotoxins explored 4 generations of drug candidates prior to the development of CAT3888 (Pastan, 2003). Incremental advances during this process included developments to the linker attaching the antibody (anti-CD22) to the toxin (*Pseudomonas exotoxin*) and the utilisation of recombinant DNA techniques to improve production of the drug (Pastan, 2003, Kreitman and Pastan, 2011). Furthermore recombinant immunotoxins presented a second generation in the history of immunotoxins in general (Teicher and Chari, 2011). A major benefit of recombinant DNA techniques is the ability to produce a smaller antibody, leading to increased efficacy whilst lowered toxicity of the drug (National Cancer Institute, 2001, Teicher and Chari, 2011).

In addition to the novelty of the immunotoxin approach the knowledge surrounding the CAT3888 target, CD22, was also relatively uncertain. Despite being found in 1987 to be expressed in B-cells (Dorken et al., 1987, Pastan, 2003) in 1997, the action of CD22 and its role in disease was described as requiring further understanding (Tedder et al., 1997).

In preclinical development CAT-3888 showed complete remissions *in vivo*, in mice models bearing lymphoma cell lines expressing CD22, with additional testing undertaken in monkey models and naked mice (Kreitman et al., 1999, Kreitman et al., 2000). Phase I trials began in 1999, where 16 patients with chemotherapy-resistant HCL were treated. The results showed 11 complete remissions, and two partial remissions (Kreitman et al., 2001a). Three of 11 patients who did relapse after 18 months showed complete remissions following retreatment (ibid).

This result demonstrated one of the main advantages of CAT-3888, over standard cytotoxins, where due to low levels of toxicities, CAT3888 can be administered in quick successions. Indeed, the toxicities in the CAT-3888 phase I HCL trial, the most severe of which was kidney failure from decreased platelet and red blood cell count, were resolved and all patients recovered showing complete remission (National Cancer Institute, 2001).

Additional phase I results also showed positive results (Kreitman et al., 2001b, Kreitman et al., 2004, Kreitman et al., 2005a, Kreitman et al., 2005b, Kreitman et al., 2008). In response to these results, and the high expectations surrounding the drug, a phase II trial in HCL patients began two years later (October 2003) (Cambridge Antibody Technology PLC, 2005a). This trial showed 16 complete responses, and eight partial responses, from a total of 35 chemotherapy-resistant HCL patients (Kreitman et al., 2009).

Whilst CAT3888 development continued, researchers at the NCI developed a second project, CAT8015, showing higher affinity to the CD22 antigen and therefore a broader range of applicability, than CAT3888, in B-cell malignancies (Kreitman and Pastan, 2011). CAT8015, was licensed along with CAT3888 from NCI, to Genencor and later to CAT, which was subsequently acquired by AZ. It was the development of CAT8015 that motivated the discontinuation of CAT3888, whereby its commercial viability was greater due to the larger market it would reach (Kreitman and Pastan, 2011, interviewee G).

Despite the success of CAT3888 in trials, incremental changes led to the development of a family of drugs, including CAT8015, with a wider potential to treat haematological malignancies. This mean that CAT3888 acted as a proof of concept for the development of a follow-up compound.

Despite the accumulated knowledge around CAT3888, there is little evidence of disease-related knowledge during the development pathway of CAT3888. This is demonstrated whereby only 2,336<sup>127</sup> articles were found to mention the primary indication (HCL) in the years leading up to trials<sup>128</sup> of CAT3888.

The therapeutic approach used in CAT3888 was novel. However, the consistency of the research group due to the majority of the work being carried out under the NCI CRADA, allowed the knowledge to accumulate throughout project development. Therefore, this should not be seen to be an inhibitory factor in the termination of the project. With this in mind and in order to maintain consistency throughout, CAT3888 is characterised as being a member of the set 'extensive and accumulated knowledge base'.

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<sup>127</sup> This figure was obtained using the Medical Subject Heading (MeSH) term 'Leukemia, Hairy Cell' as a search term in PubMed.

<sup>128</sup> Up to and including 1999

#### 7.7.4 Market demand (QCA score = 0)

The applicability of CAT3888 in cancer indications was limited by the expression of CD22 on tumour cells. By the time CAT3888 entered preclinical development it was already recognised that CD22 was only expressed B cells of human B-cell lymphomas and leukaemia (Vitetta et al., 1991, Clark, 1993, Kreitman et al., 1999). This discovery enabled the development for CAT3888 to be directed at models for B-cell malignancies found to be CD22+ (Kreitman et al., 1999, Kreitman et al., 2000). CD22 expression across all lymphomas and leukaemias stands at around 70%, and specifically at 70-85% of Non-Hodgkin's Lymphoma (NHL), 99% of B-cell CLL and more than 90% of paediatric ALL (Kreitman and Pastan, 2006).

This indicates that a large proportion of leukaemias and lymphomas express the CD22 antigen therefore providing broad applicability for CAT3888. However, the highest density of antigen sites is found in hairy cell leukaemia (10,000->100,000 per cell), where to other B-cell malignancies show 1,200 sites per cell in CLL, and 4,500 sites per cell in ALL (Kreitman and Pastan, 2011). CAT3888 demonstrated low binding affinity to CD22 indicating that HCL was the most suitable indication for the drug (Kreitman et al., 2001a, Kreitman et al., 2001b, Kreitman et al., 2004, Kreitman et al., 2008, Kreitman et al., 2005a, Kreitman et al., 2009, Kreitman et al., 2005b, Pharma Marketletter, 2005a). This realisation implied a substantial decline in the potential market demand for the drug, where HCL appears in only 2% of all leukaemia patients, totalling around 6,000 new cases each year worldwide (Maevis et al., 2014).

The small CAT3888 market potential is also echoed in press reports. In 2005, the market for the drug was quantified at between \$200-300m (Pharma Marketletter, 2005b). This can be compared to an estimate of the market for acute and chronic leukaemias which was stated, by Genencor, to stand at around \$400m in 2004, again representing a small opportunity in terms of returns for drug developers (Genencor International Inc., 2004b).

In conclusion, CAT3888 did not hold significant market potential, when considering the number of indications it could be applied to which was limited by the target receptor specificity to subtypes of leukaemias. The small market potential for CAT3888, and the higher efficacy seen in the follow-on project CAT8015, were a key contributor in the termination of the project and so the score for the QCA analysis is 0.



### 7.7.5 Stakeholder Perspectives (QCA score = 1)

CAT3888 was met with positive expectations from various stakeholders, in addition to those held by CAT, which invested in the project when they in-licensed due to the expectation that immunotoxins would be a promising area to enter into (interviewee G).

Positive drug project expectations were also felt by the scientists involved: 'the unusually high response rates led researchers to have high hopes for the use of this drug in HCL, and possibly in other patients' (National Cancer Institute, 2001). In addition scientists at competing companies also demonstrate positive perspectives where CAT3888 (previously BL22) is described as 'one of the best documented and promising immunotoxins' (Chowdhury and Wu, 2005).

Furthermore, at this time mabs, including CAT3888 (an antibody-conjugate), received high expectations from industry stakeholders. This is demonstrated in the headline, in October 2006, that stated 'Monoclonal Antibodies, Generating \$7.3 Billion in Sales in 2005, Have Been the Most Successful Class of Biological Anticancer Agents' (Research and Markets, 2006).

The investment bank, Lehman Brothers 'hailed the deal as a positive development for CAT', when the Genencor-CAT agreement was signed (Pharma Marketletter, 2005b). However, the same article estimates the potential revenues of the drug to be just \$200-300m (ibid). Furthermore, Reuters Health report the phase I findings as 'exciting for two reasons': "first, it is the second example of a targeted toxin being delivered to a specific type of tumor cell." Second... it provides further support for the use of antibodies in delivering treatments to a cancer cell' (Brown, 2001).

Patient perspectives are demonstrated, for instance, in a high profile patient story reported on CNN, presenting the project as a life-saver (Frazier, 2001). The story involved a stage four HCL patient, resistant to previously available drugs, who entered complete remission in response to CAT3888 treatment (ibid). In addition, treatment was described as 'extremely effective' and rapidly effective: 'within two days patients have more than a 90% reduction of malignant cells in their blood' (Frazier, 2001).

In terms of the stakeholder perspectives of CAT3888 it is clear that many actors saw the drug as positive, both in terms of its promising expectations, its novel nature and in the demonstration of support through patient stories. This justifies membership into the set and the QCA score of 1.

### 7.7.6 Organisational environment (QCA score = 0)

As mentioned initial development of CAT3888 was undertaken by a team at the NCI, including Pastan, Kreitman, FitzGerald and colleagues. In 2004 the NCI signed a CRADA with the US company, Genencor, for two related project candidates, BL22 (CAT3888) and HA22 (CAT8015) (Genencor International Inc., 2004a).

Genencor were a diversified biotechnology company delivering products in 'healthcare, agri-processing, industrial and consumer markets' (ibid). Genencor describes the NCI agreement as one that 'builds on our strengths in protein engineering, preclinical development, manufacturing and clinical development and on the NCI's clinical development capabilities'. This demonstrates the strategic and capability fit of the projects (CAT3888 and CAT8015) at Genencor (Genencor International Inc., 2005).

Despite this good synergy CAT3888 was only supported by Genencor for a year. In 2005 Genencor was acquired for their capabilities in industrial enzymes, by Danisco, a Danish firm focused on producing food ingredients (Danisco A/S, 2005). Shortly afterwards CAT took over the CRADA with NCI by in-licensing CAT3888 and CAT8015 (Pharma Marketletter, 2005b, Cambridge Antibody Technology PLC, 2005b).

In 2005 CAT described itself as:

'A biopharmaceutical company aiming to bring improvements to seriously ill patients' lives and in this way create outstanding returns for shareholders. The company seeks to develop high value products in which it has a significant economics interest, both independently and in collaboration with partners, by using its capabilities and technologies in the discovery and development of antibody medicines in selecting therapeutic areas. CAT also licenses its technologies to enable others to develop drugs in which CAT has a financial interest' (Pharma Marketletter, 2005a).

Despite having extensive experience in antibodies, including early research leading to Humira, a blockbuster mab approved for rheumatoid arthritis, the CAT pipeline was limited to respiratory and inflammation projects, and CAT were lacking in cancer research experience (Pharma Marketletter, 2005a). CAT's motivations for acquiring the projects were to expand activities into the USA, and into oncology and immunotoxins, both of which were perceived as areas of growth and potential (interviewee G).

The primary motivation, to expand into the USA, was fulfilled wherein CAT hired 10 key staff from Genencor to continue to be responsible for CAT3888 and CAT8015 in the USA (Cambridge Antibody Technology PLC, 2005b). In addition oncology presented the 'greatest opportunities' for firms due to: 1) medical need, 2) high numbers of relapsed or

refractory patients, 3) 'achievability' 4) multiple points for intervention (particularly in antibodies) and 5) market attractiveness (Cambridge Antibody Technology PLC, 2005a).

In 2006 CAT's commitment to oncology was further exemplified by their acquisition of an additional oncology project from Enzon (Cambridge Antibody Technology PLC, 2006). This project (CAT5001) was also an immunotoxin (using *Pseudomonas exotoxin*) that came from the lab of Ira Pastan (ibid). Therefore, CAT5001 benefitted from the capabilities accumulated during the development of CAT3888 and CAT8015. It was later announced, in 2006 that AZ was acquiring CAT (London Stock Exchange Aggregated Regulatory News Service, 2006a). The new parent company discontinued the project, as reported in their annual report in 2007 (AstraZeneca PLC, 2007).

Despite this, development of the enhanced version of the project, CAT-8015, did continue at AZ. This supports the conclusion that the reason behind the CAT3888 discontinuation was the higher potential of the follow-on, CAT8015.

This section has demonstrated that the environment surrounding CAT3888 development was positive and consistent due to the role of staff at the NCI. The consistency of the location of development and those involved in the project, may have overcome the difficulties that can be associated with mergers and acquisitions. However, the acquisition by AZ ultimately coincided with the termination of the development of CAT3888. It is this reason that contributes towards the QCA score of 0.

#### **7.7.7 CAT3888 Conclusion**

This case history indicates that the development of CAT3888 was primarily test bed used to demonstrate proof of concept, for the subsequent development of CAT8015. This highlights a mechanism of project drag distinct from those previously discussed. Here we observe a loss of momentum due to the displacement of a project as a result of the gradual gaining of momentum of another. In other words, as one proves to be more successful, the other is perceived to be relatively less so.

Project drag is compounded by the novelty of immunotoxins which was a new and uncertain approach to cancer treatment. Furthermore, while providing proof of concept, CAT3888 was aimed at a smaller patient population than its follow-on compound

(CAT8015<sup>129</sup>). The lower level of potential market demand for CAT3888 is assumed to be the main motivation for AZ discontinuing the project.

We see these factors of project drag accumulating throughout the project, becoming salient upon acquisition by AZ, whereby the acquiring firm implement a re-evaluation of the project outside of the protected space previously shielding the project, leading to termination.

## **7.8 Insights from Descriptive Analysis**

This Chapter, along with Chapter 6, has provided a lengthy discussion of the 11 drug project case histories that provide the empirical evidence for this thesis. Chapters 6 and 7 have also provided evidence justifying the QCA score which will be analysed in Chapter 8. This section builds on the conclusions drawn in Chapter 6 to formulate an overarching picture of the mechanisms contributing to success and failure of rare cancer drugs.

In our descriptive analysis of these 11 cases we refer back to the framework constructed in Chapter 3, which was further developed in the discussions of Herceptin and Gleevec, presented in Chapter 5. A diagrammatic representation of the way the data can be represented as part of this framework is presented in Figure 11. This chart not only provides summary data for the scoring of conditions for each drug project but it allows us to draw out several key trends which will be discussed in this chapter. In line with the QCA to follow, which takes explanations of success and failure to be asymmetrical, we will discuss these patterns separately for the two outcomes.

### **7.8.1 Explaining Successful Projects**

Firstly, as observed from Figure 11, successful cases all encounter at least three uppers, i.e. the mechanisms implemented to overcome issues during drug development: pazopanib encountered two downers/three uppers, nelarabine four downers/three uppers, temozolomide two downers/five uppers, Campath five downers/four uppers, and gemtuzumab five downers and three downers.

From the observation of the balance of uppers and downers, the two baseline cases, pazopanib and temozolomide, show a small number of downers, demonstrating their relatively unproblematic development pathways. Therefore, we focus our investigation

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<sup>129</sup> CAT8015, now moxetumumab, remains in development stages at AZ, entering Phase II clinical trials in 2014, and is expected to be launched in 2018 (AstraZeneca PLC, 2015)

into the mechanisms at work in the cases of nelarabine, Campath and gemtuzumab, where more downers are encountered than uppers.

One of the mechanisms used to overcome the downers in these cases is the action of key individuals. Key individuals were seen to be a substantial contributor towards the success seen in nelarabine, and Campath. In nelarabine, Trudy Elion promoted the project through mergers of the parent company and subsequent project evaluation. For Campath, Herman Waldmann and Geoff Hale helped to overcome organisational issues particularly in the wake of the Wellcome license discontinuation.

The case histories have also shown particular characteristics of key individuals that are noteworthy in promoting projects and overcoming issues in development. The two main characteristics are: 1) a strong and wide ranging network (seen to be key in nelarabine, where Elion bought in expertise from Duke University and Kurtzberg, and Campath, where Waldmann used his contacts in LeukoSite to gain a new license partner when Wellcome discontinued their involvement), and 2) continued involvement throughout the project (this is seen in nelarabine and Campath and a lack of continued involvement from key individuals was problematic in the case of banoxantrone).

Gemtuzumab also benefited from a similar mechanism of championing. In this case the organisational support was in the form of a productive and risk/benefit-sharing collaborative relationship and a good relationship between the collaborating firms' CEOs. In addition, despite the large number of downers that may have contributed towards project drag and termination, gemtuzumab also benefited from being used as proof of concept for the technological approach. Although not explicitly stated, Campath may also have been subject to this type of positive force, whereby the approach was similarly novel.

In addition, Campath and nelarabine were also aimed at areas of serious unmet medical need, whereby patient need and the lack of existing comparator for regulatory approval has a positive impact on the development of the project.

### **7.8.2 Explaining Failed Projects**

Figure 11 shows that failed projects encounter many more downers than uppers in all cases. Perhaps the least problematic case was barasertib (three downers; two uppers). In this case additional issues also arose in the lack of understanding surrounding the drug's mechanism of action, and the questions surrounding efficacy that arose gradually throughout development. Here we make two conclusions. Firstly, despite the efficacy being comparable to that found in other cases, it is perceived to be insufficient to warrant further investigation in such a small patient population. Secondly this represents

contributors to project drag, where issues accumulated causing a loss of momentum for the project.

In plevitrexed, the other unsuccessful big pharma project, again relatively low efficacy, long development times and lack of strategic fit were found to contribute towards discontinuation. Here, we find that where issues associated with projects in large firms are not resolved they contribute towards project drag. With the exception of the negative external perception of plevitrexed due to the disappointment of the precursor molecule, issues surrounding pharma drug development tend to be inherent to the project as the firm is not vulnerable to external dynamics.

In small firms, we see both the formation of protected spaces that formulate within the firms, around a project, through a process of shared positive expectations, and an undercurrent of project drag. This presents a more complex dynamic, as demonstrated in banoxantrone, TransMID, Prolarix and CAT3888.

Here the protected space may mean that the downers that contribute towards project drag are not fully recognised by the developing firm due to the suspension of objective evaluation criteria and the perception that all problems are conquerable. However, factors contributing towards the loss of momentum for the project continue to accumulate, in addition to the added complication of lack of resources, and difficulties associated with a lack of experience.

Where project drag is mainly observed to concern issues internal to the project, small firms are also vulnerable to external pressures, which may lead to M&A. Not only does M&A itself contribute towards the project drag through the disruption it causes, but it can also lead to the breakdown of the protected space and therefore the downers contributing towards project drag are uncovered.

For instance, in the cases of banoxantrone and TransMID, we observe the changes to licensing agreements and M&A events causing delays and disruptions. In addition, in banoxantrone, the blue discolouration of patients' skin also contributes to project drag. Not only would the project drag accumulate throughout development but due to the formation of protected spaces the individuals involved in development perceive these issues to be conquerable and the loss of momentum is not recognised until the protected spaces break down.

In Prolarix, we observe project drag from the delays in development, due to the changes in GMP requirements for products used in clinical trials, and the removal of the doctors and dentists exemption. This contributed towards a high burn rate for the developing firm,

which in turn led to the eventual acquisition of Enact by Protherics, and Protherics by BTG.

In CAT3888, which was displaced by CAT8015, as development progressed, the continued success of the follow-on contributed towards project drag. Here, uniquely, we find that a loss of momentum for one project is a result of the gaining of momentum in another project, providing an increasingly high benchmark comparable for the original drug.

### **7.8.3 General Observations**

In addition to the above findings associated with successful and failed projects, which highlight a difference between the dynamics in large and small firms, we also observe some general findings. Firstly, we find no direct action of patient demand on firms as was the case with Herceptin and Gleevec. This will be discussed in more detail in Chapter 9.

Another observation is the endogeneity between the issues of uncertain/novel approaches, which influence both knowledge and markets, and the enthusiasm associated with a new approach that acts to counteract the negative effects. This confirms the findings from the literature and the narratives presented in the Herceptin and Gleevec cases.

The descriptive analysis has highlighted the diversity in the mechanisms at work contributing towards success and failure of drug projects for rare cancers. This implies a complexity that makes the identification of trends difficult due to the large number of case studies assessed, necessitating an alternative methodological approach. The QCA provides this due to the ability to simplify the findings, both in terms of the calibration (scoring of membership into sets) and the amalgamation of factors into four overarching conditions. This facilitates an interpretation of the data which complements and builds on the findings from this section.

Figure 11 Representation of the framework constructed in Chapter 3, including the break down into the issues that can contribute towards a loss of momentum for the project ('project drag') under the four conditions. Cases are scored in line with the 'downers' (issues) and 'uppers' (solutions) identified in the case histories. It is evident that successful cases have more mechanisms that contribute towards overcoming issues associated with project drag, where failed drugs with some relevant solutions are highlighted in red (right hand side of the table). In projects developed by small firms some issues, such as certain external organisational dynamics, also lead to definitive go/no-go decisions, in addition to project drag

Pazopanib Barasertib Nelarabine Plevitrexed Temozolomide Campath Gemtuzumab Banoxantrone TransMID Prolarix CAT3888	Knowledge Accumulation and Base	Knowledge Transfer		Market Demand	Stakeholder Perspectives	Organisational Environment	OUTCOME									
		Novelty/Uncertain Knowledge					Low Public/User Support		Unexciting/Established Research Pathway		Vulnerability to External Dynamics		Management Changes		Strategic Fit Issues	
	Low Potential		Appropriability Issues		Novel/Uncertain Market		Low Public/User Support		Unexciting/Established Research Pathway		Vulnerability to External Dynamics		Management Changes		Strategic Fit Issues	
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## 8 Qualitative Comparative Analysis (QCA) – Crisp Set QCA

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As per the methodological approach set out in Chapter 4, a QCA was undertaken in addition to the descriptive analysis carried out in Chapters 6 and 7. While the descriptive analysis built up the similarities and differences between each case, the results from this QCA provide a comparative analysis of all of the projects seen together. The QCA findings are complementary to previous findings because the previous descriptive analysis provided a dynamic view of the case histories, while the QCA will take an overall picture of the project, rather than appreciate changes through time.

The QCA findings echo those from the descriptive analysis: the main condition associated with success is a supportive organisational environment. Here, the QCA shows that this condition is necessary, but not sufficient, in isolation, for the success to occur. In addition, in conjunction with the presence of either, positive stakeholder perspectives, or an extensive and accumulated knowledge base, a supportive organisational environment is sufficient for success. Furthermore, interestingly a high market demand is not required to confer success (as seen in the cases of nelarabine and gemtuzumab).

Due to the asymmetric nature of QCA, explaining the absence of the outcome (i.e. non-technical<sup>130</sup> failure of a project) warrants separate analysis. Here, the QCA findings indicate that failure is associated with the absence of a high market demand (a necessary condition), in conjunction with either the absence of a supportive organisational environment, or the absence of an extensive and accumulated knowledge base and the absence of positive stakeholder perspectives<sup>131</sup>.

Throughout this thesis, as mentioned in Chapter 4, an upper case letter is represents the presence of a condition, and a lower case letter the absence of a condition, as is common practice in the implementation of QCA methodology.

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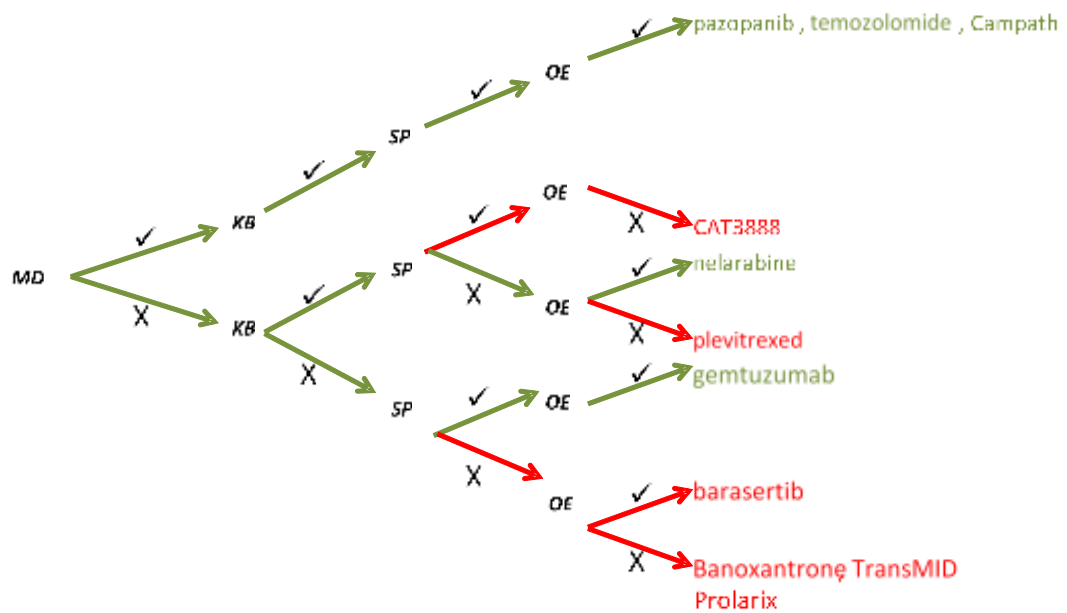
<sup>130</sup> Recall here that the research design excluded cases terminated for technical reasons, i.e. those due to safety, or severe efficacy (i.e. the drug was found to show very little or no response in patients).

<sup>131</sup> The terminology in this thesis, is in-line with QCA good practice. Due to the nature of the calibration of the conditions, it is more suitable to discuss the presence/absence of a condition, as opposed to substituting in different descriptors (e.g. high/low, unaccumulated/accumulated, positive/negative, supportive/unsupportive). This was discussed in section 4.4.3.

## 8.1 Summary of Crisp Set QCA Scores

QCA scores<sup>132</sup> were assigned for each condition (extensive and accumulated knowledge base, high market demand, positive stakeholder perspectives and supportive organisational environments) in the case histories presented in Chapters 6 and 7 (summary of data points and justification of QCA score in Table 31).

Prior to undertaking the QCA we can make some initial observations from the different projects pathways, and how these differentiate successful (green) and unsuccessful (red) outcomes. These are presented in diagram (Figure 12) and table format (Table 32). Figure 12 supports the premise that organisational environment differentiates success from failure. When tabulated (Table 32), with darker shaded cells indicating where observed score is different to that expected (under the assumption that all four conditions are required for success), the deviant, and therefore interesting, cases are: nelarabine, barasertib, plevitrexed, gemtuzumab and CAT3888.



**Figure 12** Typology diagram representing the pathways represented in the empirical data

<sup>132</sup> QCA scores are mentioned at the end of each section in Chapter 6 and 7.

Table 31 Summary of data used to justify QCA scores for case histories

Drug Project	Extensive and Accumulated Knowledge Base						High Market Demand						Positive Stakeholder Perspectives				Supportive Organisational Environment					Y
	Targeted or Cytotoxic	New/ Established	Target Validated	Consistent Research Team	Disease Knowledge	QCA	Many Indication	Media Report	Competitor	Orphan Drug status	Patent Issues	QCA	Positive Media Reports	Easy Administration	Patient Stories	QCA	Interorg. Activity	Productive Relationship	Strategic	Experienced Firm	QCA	
Pazopanib	Targeted	New	Yes	Yes	No	1	Yes, common	~\$1bn per year	Sunitinib (3 yrs prior)	No	No	1	Yes	Yes	No	1	No (mergers early on)	n/a	Yes	Yes	1	1
Barasertib	Targeted	New	No	Yes	Yes	0	No	n/a	Gem-tuzumab (before)	No	No	0	Not of project	No	No	0	Yes (discovery phases)	n/a	Yes	Yes	1	0
Nelarabine	Cytotoxic	Established	Yes	Yes	Yes	1	No	\$1bn	No	Yes	No	0	Not of project	No	No	0	Yes	Yes, also internal key individual	No	Yes	1	1
Plevitrexed	Cytotoxic	Established	Yes	Yes	Yes	1	Yes, common	\$12m; \$8m; \$66m		Yes	Yes	0	Not of project	No	No	0	Yes	Yes and no	No	Yes	0	0
Temo- zolomide	Cytotoxic	Established	Yes	Yes	Yes	1	Yes, common	n/a	No	Yes	No	1	Yes	Yes	Yes	1	Yes (commercial)	n/a	Yes	Yes	1	1
Campath	Targeted	New	No	Yes	Yes	1	Yes, common	n/a	No	Yes	No	1	Yes	No	No	1	Yes	Yes	Yes	Yes and no	1	1
Gem- tuzumab	Targeted	New	No	Yes	Yes	0	No	\$300m; \$250m; \$150m	No	Yes		0	Yes	No	Yes	1	Yes (discovery phases)	Yes	Yes	Yes and no	1	1
Banox- antrone	Targeted	New	No	No	No	0	Yes (not developed)	\$250m		No	No	0	Yes (but blue side effect)	No	No	0	Yes	Yes and no	No	No	0	0
TransMID	Targeted	New	No	Yes and no	Yes	0	No	\$600m; \$210m	Carmustine implant/ temo- zolomide	No	Yes	0	Yes	No	No	0	Yes	Yes and no	Yes	No	0	0
Prolarix	Targeted	Established	No	No	No	0	No	\$2.8bn; \$250m	Sorafenib (not NICE approved)	No	No	0	Yes (limited & local)	No	No	0	Yes		No	No	0	0
CAT3888	Targeted	New	No	Yes	No	1	No	\$200-300m	No	No	No	0	Yes	No	Yes	1	Yes	Yes	No	Yes	0	0

Case ID	Knowledge	Market	Stakeholders	Environment	Outcome
Pazopanib	1	1	1	1	1
Nelarabine	1	0	0	1	1
Barasertib	0	0	0	1	0
Plevitrexed	1	0	0	0	0
Temozolomide	1	1	1	1	1
Campath	1	1	1	1	1
Gemtuzumab	0	0	1	1	1
Banoxantrone	0	0	0	0	0
TransMID	0	0	0	0	0
Prolarix	0	0	0	0	0
CAT3888	1	0	1	0	0

**Table 32 Summary of csQCA scores for each drug project case study (green for successful pathways, red for unsuccessful pathways; darker colour for where presence/absence of condition does not correspond with presence/absence of outcome)**

## 8.2 Analysis

The first stage of a QCA is to assess necessary conditions. This is followed by the construction of a truth table, and the generation of solutions presenting the configurations explaining the outcomes. Each of these analyses are undertaken separately for successful and unsuccessful outcomes, due to the asymmetrical nature of QCA.

### 8.2.1 Necessity – Explaining Successful and Unsuccessful Cases

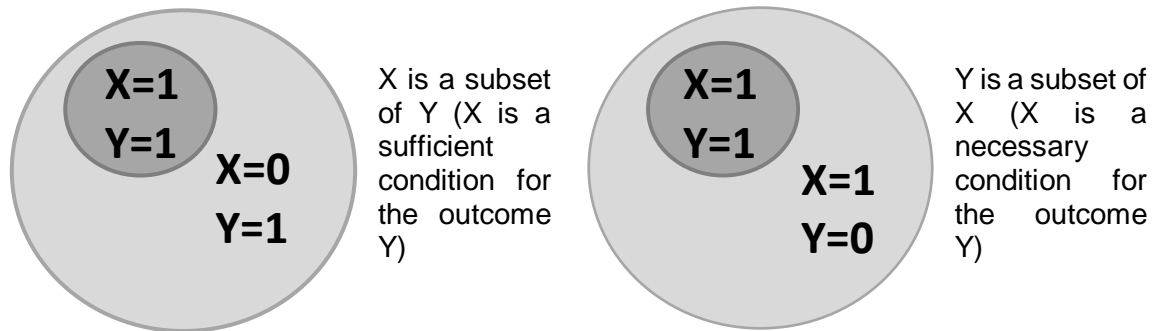
A condition is found to be sufficient when there are cases showing presence of the condition and presence of the outcome, (cases in  $X^{133}=1, Y=1$ ), while no cases show presence of the condition and absence of the outcome (no cases in  $X=1, Y=0$ ). Cases with  $X=0, Y=1$ , or  $X=0, Y=0$  are irrelevant. This is because sufficiency is found when the condition (X) in question is a subset of the outcome (Y) (Figure 13). In other words, the presence of the condition would be sufficient for the outcome to occur, or 'if X, then Y'.

In contrast, for a condition to be necessary for the outcome to occur, there should be cases that show the presence of the condition and the outcome (cases in  $X=1, Y=1$ ), and no cases where there is the absence of the condition and the presence of the outcome

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<sup>133</sup> X in general discussions of QCA methodology, represents the condition score, where Y represents the outcome.

(no cases in  $X=0, Y=1$ ). This is because the outcome (Y) is a subset of the condition (X) (Figure 13).



**Figure 13 Venn diagram illustrating the relationship between subset/superset relationships and necessity and sufficiency**

This section explores the necessity of each condition for successfully advancing a project to regulatory approval. This assessment is facilitated by the construction of matrices for each condition. Each condition is represented by a letter, knowledge base, 'B', market demand, 'D', stakeholder perspectives, 'S' and organisational environment, 'E'<sup>134</sup>.

These matrices (see Table 33, Table 34, Table 35, and Table 36) indicate that a supportive organisational environment is necessary for the outcome to occur. This is confirmed in when a test of necessity is computed (Table 37).

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<sup>134</sup> These letters were chosen due to the obvious distinction between the upper and lower case letters.

***B (extensive and accumulated knowledge base)***

		0	1	
Y	1	gemtuzumab	pazopanib, nelarabine, temozolomide, Campath, gemtuzumab	Extensive and accumulated knowledge base is neither necessary (due to the presence of gemtuzumab) nor sufficient (due to the presence of plevitrexed)
	0	barasertib, banoxantrone, TranMID, Prolarix,	Plevitrexed, CAT3888	

**Table 33 Matrix identifying necessity and sufficiency of extensive and accumulated knowledge base*****D (high expected market demand)***

		0	1	
Y	1	nelarabine, gemtuzumab	pazopanib, temozolomide, Campath	High expected market demand is sufficient (due to the absence of cases in X=1, Y=0), but not necessary due to the presence of cases in Y=1, X=0
	0	barasertib, plevitrexed, banoxantrone, TranMID, Prolarix, CAT3888		

**Table 34 Matrix identifying necessity and sufficiency of high market demand*****S (positive stakeholder perspectives)***

		0	1	
Y	1	nelarabine	pazopanib, temozolomide, Campath, gemtuzumab	Positive stakeholder expectations is neither sufficient (due to the presence of TransMID and CAT3888) nor necessary (due to the presence of nelarabine) for the success to occur
	0	barasertib, plevitrexed, banoxantrone, TransMID, Prolarix	CAT3888	

**Table 35 Matrix identifying necessity and sufficiency of positive stakeholder perspectives*****E (supportive organisational environment)***

		0	1	
Y	1		pazopanib, nelarabine temozolomide, Campath, gemtuzumab	A supportive organisational environment is necessary (due to the absence of cases in the Y=1;X=0 cell) but not sufficient for success to occur (due to the presence of barasertib)
	0	plevitrexed, banoxantrone, TransMID, Prolarix, CAT3888	barasertib	

**Table 36 Matrix identifying necessity and sufficiency of supportive organisational environment**

Condition	Consistency	Coverage
B	0.8	0.67
b	0.2	0.2
D	0.6	1
d	0.4	0.25
S	0.8	0.8
s	0.2	0.17
E	1	0.83
e	0	0

**Table 37 Consistency and coverage values for necessary conditions to explain successful cases**

The necessity of a supportive organisational environment for success, further demonstrating the key points identified from the descriptive analysis. In order for success to occur, a supportive organisational environment should be present. However, it is also possible for the presence of a supportive organisational environment to appear in failed projects (e.g. in the case of barasertib), because the condition is necessary but not sufficient for success. In addition, despite the matrix analysis apparently showing that a high market demand is sufficient for success, a truth table analysis is required to confirm this.

Due to the asymmetrical nature<sup>135</sup> of QCA an analysis of necessary conditions is also undertaken for the absence of the outcome (i.e. failure/unsuccessful projects). In this instance as there are no obvious (100%) necessary conditions, therefore it is helpful to compute calculations to ascertain necessary conditions for the absence of success (Table 38). In this, consistency is a measure of the extent to which the empirical data are represented by the measure of necessity, i.e. the degree to which the outcome can be considered as a subset of the condition (Schneider and Wagemann, 2012:143). Coverage represents the relevance of the necessity of a condition. Therefore, in order for necessity to be concluded, both consistency and coverage scores should be high (Schneider and Wagemann, 2012:147).

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<sup>135</sup> The asymmetric nature of QCA implies that the conditions associated with failure are not necessarily the counter scenario from those seen in successful cases

Condition	Consistency	Coverage
B	0.33	0.33
b	0.67	0.8
D	0	0
d	1	0.75
S	0.17	0.2
s	0.83	0.83
E	0.17	0.17
e	0.83	1

**Table 38 Consistency and coverage values for necessary conditions to explain unsuccessful cases**

Table 38 indicates that, although not perfect, the absence of a high expected market demand is found to be necessary for an unsuccessful outcome. This is concluded due to a consistency value of 1, representing a coverage of 75% of cases.

### **8.2.2 Truth Table Analysis – Explaining Successful Cases**

A truth table (Table 39) is constructed where all possible combinations of conditions are accounted for, either where empirical cases exist, or a configuration is a logical remainder, where cases are not observed. The objective of a truth table is to define which configurations are relevant to include in the solution formulation, where the solution represents the pathway(s) leading to the outcome. We assign configurations to include as '1', if evidence shows that this configuration leads to the presence of the outcome, '0' to exclude, if evidence indicates this configuration leads to the absence of the outcome, and logical remainders as '-'.

In this section we will analyse successful cases, and therefore include configurations observed in the successful empirical cases. Initially, if the empirical case is not observed, the configuration is not included (Table 39).



B	D	S	E	Cases (outcome)	Consistency	Inclusion
1	1	1	1	pazopanib (1), temozolomide (1), Campath (1)	1	1
1	1	1	0	-		-
1	1	0	0	-		-
0	1	0	0	-		-
1	0	1	0	CAT3888 (0)		0
0	0	1	1	gemtuzumab (1)	1	1
1	1	0	1	-		-
0	1	1	1	-		-
0	1	1	0	-		-
0	1	0	1	-		-
1	0	1	1	-		-
1	0	0	1	nelarabine (1)	1	1
1	0	0	0	plevitrexed (0)	0	0
0	0	1	0	-		-
0	0	0	1	Barasertib (0)	0	0
0	0	0	0	banoxantrone (0), Prolarix (0), TransMID (0),	0	0

**Table 39 Truth table explaining a successful outcome, with no assumptions made about counterfactuals**

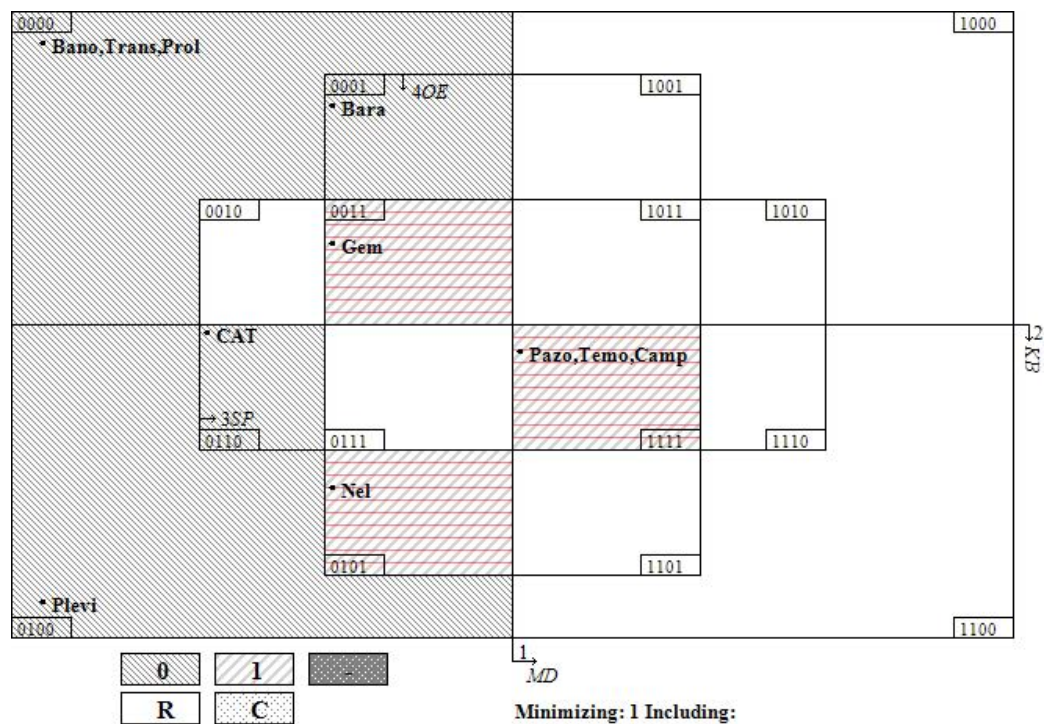
In the absence of any approach to deal with logical remainders the solution, after logical minimisation, based solely on the empirical data is<sup>136</sup>:

$$BdsE + bdSE + BDSE \longrightarrow Y \quad (\text{solution 1a})$$

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<sup>136</sup> Note that with Boolean algebra '+' represents 'or'

This can be presented as a Venn diagram (Figure 14).



**Figure 14 Venn diagram showing truth table analysis explaining success**

Solution 1a shows that success is associated with either i) a presence of extensive and accumulated knowledge base, absence of high expected market demand, absence of positive stakeholder expectations and presence of supportive organisational environments, or ii) the extensive and applicable knowledge base and absence of high expected market demand, and the presence of positive stakeholder expectations and the presence of supportive organisational environment, or iii) the presence of all four conditions, in conjunction.

However, this solution is too complex to be informative. This complexity arises from limited diversity existing in social reality, meaning that only a limited number of possible combinations are empirically observed (Schneider and Wagemann, 2012:152-3). To combat this, in a QCA analysis, we can account for counterfactuals, by predicting the outcome that would occur in observed configurations.

We observe BDSE (pazopanib, temozolomide, and Campath), bdSE (gemtuzumab) and dBsE (nelarabine) in the empirical data. Therefore, can also infer that BdSE, BDsE and bDSE, if observed, would also account for success, and so should be included into the truth table analysis. The configuration bDSE is also further supported by the case history of Herceptin. We can therefore re-run the truth table including these additional configurations ('1' in Table 40).

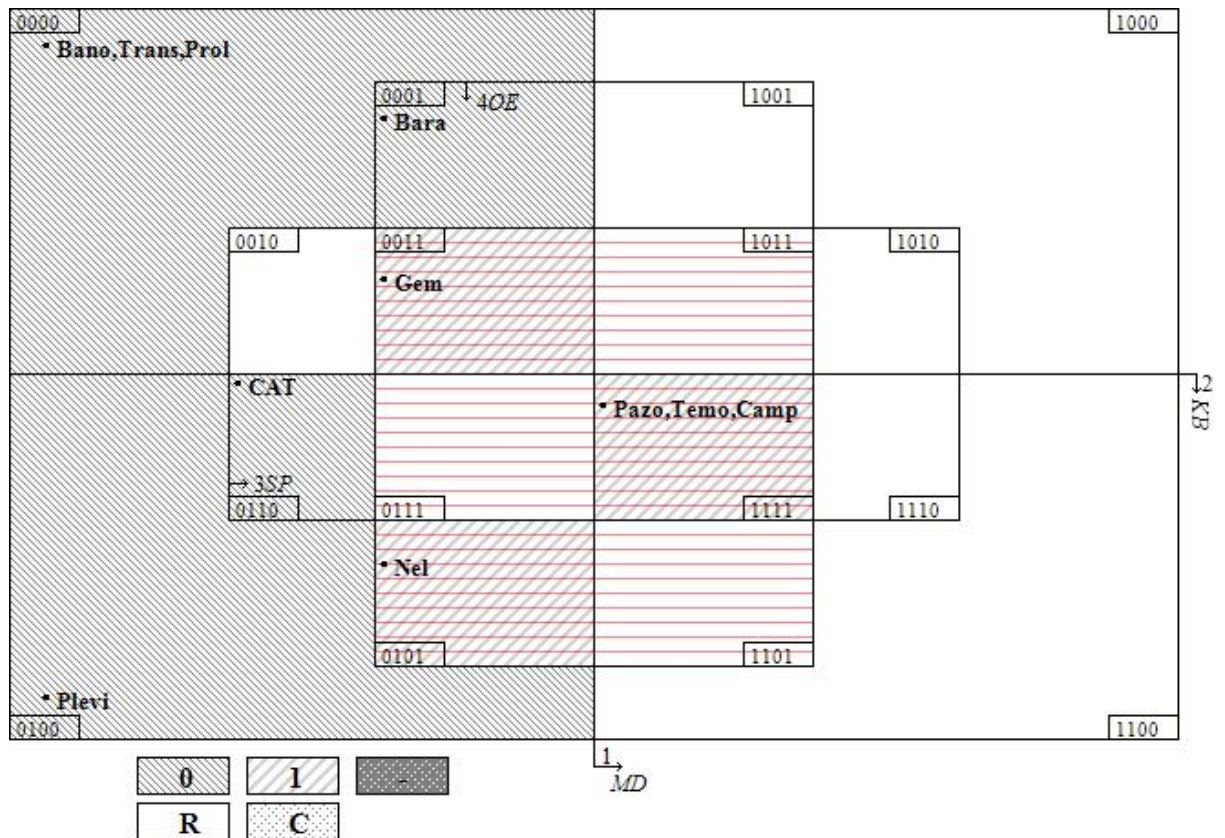
B	D	S	E	Cases (outcome)	Consistency	Inclusion
1	1	1	1	pazopanib (1), temozolomide (1), Campath (1)	1	1
1	1	1	0	-		
1	1	0	0	-		
0	1	0	0	-		
1	0	1	0	CAT3888 (0)	0	0
0	0	1	1	gemtuzumab (1)	1	1
1	1	0	1	-		<b>1</b>
0	1	1	1	-		<b>1</b>
0	1	1	0	-		
0	1	0	1	-		
1	0	1	1	-		<b>1</b>
1	0	0	1	nelarabine (1)	1	1
1	0	0	0	plevitrexed (0)	0	0
0	0	1	0	-	0	0
0	0	0	1	Barasertib (0)	0	0
0	0	0	0	banoxantrone (0), Prolarix (0), TransMID (0)	0	0

**Table 40 Truth table explaining a successful outcome, with assumptions made about counterfactuals**

The resulting solution, after logical minimisation is:

$$BE + SE \longrightarrow Y \quad (\text{solution 1b})$$

When representing solution 1b as a Venn diagram it accounts for a logical portion of the space, including all the empirical instances where the outcome is observed (Figure 15).



**Figure 15 Venn diagram showing truth table analysis explaining an unsuccessful outcome**

Interpreting solution 1b shows that in order for the outcome (success) to occur a project requires supportive organisational environment, in combination with either i) the presence of extensive and accumulated knowledge base, or ii) the presence of positive stakeholder expectations, irrespective of the presence or absence of extensive and accumulated knowledge base and high expected market demand.

In other words, whenever a supportive organisational environment occurs, so will success, assuming the drug has the potential to work<sup>137</sup>. However, a supportive organisational environment can occur in the case of unsuccessful drugs (for instance, in the case of barasertib) because the condition (OE) needs to be combined with other conditions (in this case either an extensive and accumulated knowledge base, or positive stakeholder support).

<sup>137</sup> This was fulfilled in the selection of the cases and the focus on projects that had failed for non-technical reasons (i.e. safety and/or severe efficacy). Refer to Chapter 4, section 4.4.2.2.2.

Although not conclusive, due to the lack of cases observed showing the presence of a high market demand, it is intuitive, and not contradicted by the empirical data that a high market demand is sufficient, on its own, to lead to success. More data would be needed to prove this conclusively suggesting an avenue for future research whereby projects for larger population sizes may provide further insights. This was not addressed in this thesis due to an ambition to understand and compare cases aimed at small markets. This also facilitated a bounding of the research in line with feasibility, as the sample size would have grown substantially if all cancer indications were included.

The solution explaining success is also interesting because stakeholder expectations, such as those associated with patient stories, contribute to the outcome in association with supportive organisational environments, despite the possible absence of extensive and accumulated knowledge base. Similarly, the presence of extensive and accumulated knowledge base, in the presence of supportive organisational environments can, on its own, contribute towards success despite the absence of positive expectations amongst wider stakeholders.

### 8.2.3 Truth Table Analysis – Explaining Unsuccessful Cases

Due to the asymmetrical nature of the results obtained from a QCA, we use a separate truth table analysis to explain the absence of the outcome, i.e. unsuccessful projects. This uses the same data as the previous analysis but includes, into the solution, the cases associated with the absence of the outcome. Here, the software is instructed to explain the negated outcome ( $y$ ) with the resulting truth table representing the consistency scores for each configuration (related to the outcome scores for the cases included).

Without accounting for logical remainders, this analysis show the resulting solution:

$$bds + Bde \longrightarrow y \quad (\text{solution 2a})$$

As we did in the analysis of the successful outcome, we use logic to account for logical remainders, using simplifying assumptions. In this we can assume that as BdSe is associated with an unsuccessful project then it is likely that bdSe will also equate to the absence of the outcome (Table 41). Furthermore, as with the analysis of the successful outcome, here we also need to ensure that no configurations showing the absence of the necessary condition (the absence of high market demand) are not considered in counterfactuals contributing towards explaining the presence of the outcome we want to explain (in this case the absence of success) ('0' in Table 41).

B	D	S	E	Cases (outcome)	Consistency	Inclusion
1	1	1	1	pazopanib (1), temozolomide (1), Campath (1)	0	0
1	1	1	0	-	-	0
1	1	0	0	-	-	0
0	1	0	0	-	-	0
1	0	1	0	CAT3888 (0)	1	1
0	0	1	1	gemtuzumab (1)	0	0
1	1	0	1	-	-	0
0	1	1	1	-	-	0
0	1	1	0	-	-	0
0	1	0	1	-	-	0
1	0	1	1	-	-	-
1	0	0	1	nelarabine (1)	0	0
1	0	0	0	plevitrexed (0)	1	1
0	0	1	0		-	1
0	0	0	1	Barasertib (0)	1	1
0	0	0	0	banoxantrone (0), Prolarix (0), TransMID (0)	1	1

**Table 41 Truth table explaining an unsuccessful outcome, with assumptions made about counterfactuals**

The resulting solution is:

$$de + bds \longrightarrow y \quad (\text{solution 2b})$$

This solution highlights that unsuccessful cases are associated with a lack of market demand and either 1) the absence of supportive organisational environments, or 2) the absence of extensive and applicable knowledge base and positive stakeholder perspectives. In other words, whenever a lack of market demand occurs a drug is unsuccessful. However, as seen in the cases of gemtuzumab and nelarabine, a lack of market demand can occur in association with success. This is because a lack of demand is necessary (i.e. the outcome is a subset of the condition) and needs to be combined with other conditions in order to account for all empirical cases.

Despite solution 2b appearing to show contradictions from the complex solution 2a, that makes no conclusions about counterfactuals/logical remainders, in terms of the presence/absence of an extensive and accumulated knowledge base, it is intuitive that solution 2b be more akin to reality. Here we consider that, where solution 2a includes the presence of extensive and accumulated knowledge base ('B') in one of the pathways explaining an unsuccessful outcome ('y'), it is more logical, with our knowledge of the process of drug discovery and development, that the absence of an extensive and

accumulated knowledge base ('b') should be associated with an unsuccessful outcome ('y'), as presented in solution 2b<sup>138</sup>.

Furthermore, if we exclude the atypical case, CAT3888, which was discontinued due to its role as a tool for proof of concept, rather than a drug development endeavour in its own right, the resultant complex solution (i.e. with no simplifying assumptions accounting for logical remainders). This supports the role of absence of extensive and accumulated market demand in explaining failure.

$$dse + bds \longrightarrow y \quad (\text{solution 2c})$$

### 8.3 Summary of QCA Findings

The QCA analysis has shown that in successful projects, organisational environment plays a key role and is necessary for the outcome to occur. This corresponds to the explanation from the descriptive analysis section which highlights the importance of organisational relationships, and the action of key individuals to the promotion of the success of a project. The resulting solution (solution 1b) is taken to be explanatory for the outcome to occur. Here for ease of interpretation we can factor out the necessary role of a supportive organisational environment

$$E(B + S) \longrightarrow Y \quad (\text{solution 1b})$$

In the case of unsuccessful (or in the absence of success) projects a key role is played by market potential. In isolation, however, this is not sufficient for a project to be discontinued. When a lack of high market demand coexists with unsupportive organisational environments, or with limited knowledge and a lack of positive stakeholder perspectives, a project is unlikely to succeed. In solution 2b we can factor out the necessary role of an absence of market demand, for interpretations sake.

$$d(e + bs) \longrightarrow y \quad (\text{solution 2b})$$

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<sup>138</sup> Incidentally, it is common and, in fact, good practice to refer back to theoretical and empirical knowledge when assessing the suitability of different solution options.

## **8.4 QCA Discussion**

The QCA analysis echoed the findings from the descriptive analysis in the finding that a supportive organisational environment is often key to driving the success of a project. In explaining success, this factor is a necessary inclusion in the pathway to success. This finding is interesting because it highlights that a project may succeed regardless of the level of expected market demand. For instance, in gemtuzumab and nelarabine, other factors such as the role of key individuals, managerial support, fulfilling unmet medical need and productive collaborative relationships, overcame the role of market demand. This contrasts to the accepted perspective that markets are central issue in accounting for whether or not a project is continued.

The solution outputs to a QCA should be interpreted in configurations, as well as the necessary role of single conditions. Here we explore each pathway contributing towards each outcome, i.e. BE and SE for success, and de and dbs for failure, and will focus on the deviant cases i.e. not BDSE for success (pazopanib, temozolomide, Campath) or dbse for failure (banoxantrone, Prolarix, TransMID).

In success, supportive organisational environments appear to be sufficient when combined with other conditions. Firstly, when combined with positive stakeholder perspectives, supportive organisational environments account for gemtuzumab. Here the path to success involved the action of heavily publicised patient stories, a productive collaborative relationship between the organisations and Celltech's lack of vulnerability to the funding environment.

Alternatively, the conjunction of extensive and accumulated knowledge base with supportive organisational environments explains the pathway leading to success in nelarabine. Nelarabine was based on an established knowledge trajectory and a consistent research team, in addition to being supported by a key individual and aimed at an unmet need which helped to counteract proposals to terminate the drug's development by BW, and later, GW.

In explaining unsuccessful projects, the absence of a high market demand was found to be necessary for the outcome, and sufficient when in conjunction with either the absence of supportive organisational environments, or the absence of extensive and accumulated knowledge base and the absence of positive stakeholder perspectives. Here, although it was common to see successful projects developed regardless of market potential (e.g. in the cases of gemtuzumab and nelarabine), there are no instances in which an unsuccessful outcome shows a high market demand.



The path contributing towards an unsuccessful outcome accounts for plevitrexed and CAT3888 ( $de \rightarrow y$ ) and barasertib ( $bds \rightarrow y$ ). For plevitrexed the outcome was associated with a lack of potential/expected market demand, organisational communication difficulties and a lack of strategic cohesion between project and organisation (AZ). In barasertib, the outcome can be explained by insufficient market demand, false predictions/uncertainty surrounding the knowledge foundation and lack of media/stakeholder coverage.

## 9 Discussion and Conclusions

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### 9.1 Summary of Findings

This thesis provides an extensive discussion of the conditions associated with success and failure of rare cancer drug development projects. This investigation was motivated by the health burden of cancer, and the need for new therapeutics to treat patients. The investigation into rare cancers is further justified by the shifts in the approaches to both drug discovery and development, particularly in oncology, and the associated changes to the strategies and structure of the industry. The drug development project itself is taken as the unit of analysis in order to enable a holistic narrative of the factors influencing the outcome, regardless of the changes and movement of the project from organisation to organisation and through its life cycle.

The context Chapter (2) presented a review of the empirical history surrounding cancer research and the drug development process. The literature discussing the forces of biomedical innovation were also reviewed, highlighting the relevance of a multi-dimensional approach and facilitating the construction of a framework, later used to aid data collection and analysis. This chapter also illustrated the significance of the present research justifying it in the context of an industry in flux, with the introduction of personalised medicine, particularly in the context of oncology therapeutics, and the increasing costs and need for efficiencies to be achieved. This changing system warrants the reassessment of business models, policies and strategies surrounding the development of drugs for the modern age, which in turn require an investigation into the key conditions affecting the successful and unsuccessful production of drugs.

The literature review facilitated an exploration into the effect of conditions on innovation in different sized firms, and the associated resource constraints. In addition, the importance of the access and integration of knowledge, both within and between firms, and dynamics of inter-firm relationships was also emphasised. We discussed the importance of key individuals active in promoting projects, and thereby influencing innovation and the role of individuals in their surrounding networks. Finally, we highlighted the importance of expectations in the development of drugs. Here, it was emphasised that innovations are a function of individuals' actions and the expectations they hold. In addition, protected spaces (discussed in Chapter 3, section 3.2.3), created by collective expectations shared by a group can influence the interpretation of results, thereby clouding judgement and, in some cases, contributing towards the suspension of evaluation criteria (Konrad, 2006).

A literature gap was identified, wherein there is a lack of studies of drug innovation focusing on the project as the unit of analysis. In addition, the literature tended to focus on one or two of the dimensions (individuals, organisations, networks) surrounding drug development. In order to fill these gaps this thesis had the objective of addressing the question: *why do some drug projects succeed in development, while others fail?* It was appreciated early on that this question was broad ranging and required some deconstruction. Therefore, the following questions were posed: *what environmental (socio-economic) conditions, identified from the innovation literature, influence go/no-go decisions in drug development?* This objective was fulfilled by the literature review and construction of the framework. Further, *how do the environmental (socio-economic) conditions, identified from the framework, contribute towards the development of rare cancer drug projects?* This question was answered in the analyses, the findings from which are described below. The final question: *do these conditions show interactions and/or cumulative causality (project drag)?* refers to the interactive dynamics of conditions influencing drug development. Here we are interested in whether particular conditions, or factors contribute terminally to an outcome, or whether they have the cumulative effect of causing the project to gradually lose momentum and fail.

In order to answer these questions, it was realised early on, in line with much of the literature in this area, that it was necessary to undertake a case study approach. This thesis had the added aim of providing a degree of generalisation facilitated through the implementation of a multiple case study method was implemented. This involved undertaking a descriptive comparative analysis and a QCA, within the context of theory building. QCA has facilitated a systematic, and case-based view of the empirical evidence in this thesis appreciating the multiple configurations leading to success and failure.

The selection and investigation of 11 drug project case histories enabled a detailed description of the systems surrounding drug development, the forces at work and the reasons behind termination or success. The case histories were contextualised in a pilot study of path breaking drugs which were well documented and used both to demonstrate examples of causal pathways as well as to test the utility of the framework.

In line with the differences in drug development between large and small firms, identified from the literature review, the 11 case histories were grouped accordingly. This division highlighted one of the first findings of this thesis. We observe that in projects from big pharma, drugs tend to be subject to 'project drag'. Here, we witness the accumulation of issues, observed through evaluation processes, such as market potential (barasertib),

sufficient efficacy (barasertib, plevitrexed), or lack of strategic research direction (plevitrexed). Furthermore, in large firms organisational environment is found to be relatively supportive, thereby proving an unproblematic condition, this can contrast sharply with circumstances in smaller firms<sup>139</sup>. This is unsurprising due to large firms' broad-ranging capabilities, abundant resources, economies of scale and scope as well as experience in accessing and integrating internal and external knowledge, as was highlighted in the literature review. Here, we only see one case whereby the organisational environment is deemed to be insufficiently supportive in a large firm, where the strategic fit of the project, along with other issues, contributed to development termination. Contrastingly, small firms tend to be more vulnerable to external forces, limiting access to resources, and expertise.

Drugs developed by small biotech firms were subject to more complex industrial dynamics due to their vulnerability to organisational issues, where firms underwent an unexpectedly large number of transactions, and the formation of protected spaces. However, issues contributing towards project drag, such as delays, efficacy issues, and M&A and license change disruptions were also apparent.

The descriptive analysis allowed us to explore mechanisms implemented to overcome issues contributing towards project drag. Key individuals were found to have a role in mediating project development through promoting drug progress (Campath, nelarabine, and temozolomide). Unmet need (gemtuzumab, temozolomide and nelarabine), novel technological approaches (gemtuzumab and Campath) and public/charity support (temozolomide) were also found to play a role in motivating drug development within firms.

The QCA sought to confirm and expand on the findings from the descriptive analysis. This highlighted that the role of a supportive organisational environment is necessary for success, implying that, whenever the outcome is present (success), supportive organisational environments are also present. However, this condition is not sufficient for success and relies on the presence of either an extensive and applicable knowledge base, or positive stakeholder perspectives to contribute towards the successful development of a project (solution 1b:  $E(B+S) \rightarrow Y$ ).

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<sup>139</sup> This is with the exception of plevitrexed where the cytotoxic action of the drug was not aligned with the organisation's strategy (moving towards targeted therapeutics).

Due to the asymmetrical nature of a QCA a separate assessment of the role of the explanatory conditions on the absence of the outcome (failure) was undertaken. It was found that an absence of market demand was necessary for an unsuccessful outcome. However, in order to fully explain failure, pathways involving a conjunction of factors had to be explored. Failure is associated with an absence of market demand and either 1) the absence of a supportive organisational environment; or 2) the absence of an extensive and accumulated knowledge base and a lack of positive stakeholder perspectives (solution 2b from Chapter 8:  $d(e+bs) \rightarrow y$ ).

It is most surprising that having an extensive and accumulated knowledge base did not independently play an important role explaining either success or failure. The deviant cases contradicting the action of this condition are plevitrexed and CAT3888, where a knowledge base is detected but this is not met with success, and gemtuzumab, where a well-developed knowledge base was absent but the project succeeded. The former cases can be explained through the consideration of their role within the portfolio of the host firm.

Firstly, plevitrexed was a follow-on and part of a traditional approach to drug discovery and development (cytotoxins), and therefore subject to stringent evaluation due to the lack of strategic position in the firm's pipeline. Secondly, CAT3888, did have an accumulated knowledge base but to a large extent the purpose of the project was to provide proof of concept, and an understanding of the drug target and interactions, for the follow-on. Gemtuzumab benefited from other motivations (e.g. desire for proof of concept) and therefore the stakeholders involved in developing the drug mobilised resources to overcome issues resulting from lack of knowledge in particular areas (for instance, in the development of the mab/toxin linker).

## **9.2 Theoretical Contributions**

Primarily, this thesis' contribution is in answering the empirical research questions. In particular, the first and second questions are addressed by the identification of the conditions influencing drug innovation for rare cancers. Four conditions (knowledge base, market demand, stakeholder perspectives and organisational environment) were identified through an in-depth review of the literature, all of which were found to play a role in the development of these drugs. We find that safe and effective drugs may not be developed despite potentially providing a benefit to patients, indicating that the market does not function adequately and that other factors also play a role.

The third research question explored the utility and relevance of the term 'project rag' and concluded that drug projects do experience project drag, i.e. the accumulation of issues

contributing towards the loss of momentum for the drug. In small firms this interacts with the influence of protected spaces (section 3.2.3). Here termination appears to be a result of definitive decision making, usually resulting from the impact of external pressures, but also the accumulation of project drag that lies latent until the breakdown of collective expectations (protected spaces) leading to re-evaluation (for further discussion see section 9.2.2).

### 9.2.1 Role of Supportive Organisational Environment

The condition found most consistently to play a role in defining innovation outcomes is that of a supportive organisational environment, as evidenced from the descriptive analysis and QCA. The identification, from the QCA, of the necessity of the presence of this condition for success is important because necessary conditions lend themselves to policy interventions (Ragin, 2000). We therefore conclude that all instances of successfully developed projects will show the presence of a supportive organisational environment. However, we also note that in order to fully confer success, this condition needs to appear alongside other conditions (an extensive and accumulated knowledge base and/or a positive stakeholder perspective).

The organisational environment also plays a role in the failure of drug projects. Here, a difficult organisational environment is a component of the pathway to failure, in combination with the perception of relatively low market potential. By looking at the pathways to failure ( $db\bar{s} + d\bar{e} \rightarrow y$ ), we observe that  $db\bar{s}^{140}$ , i.e. the absence of: 1) market demand, 2) extensive and accumulated knowledge base and 3) positive stakeholder support, only uniquely accounts for one case, barasertib. All other failures resonate more with  $d\bar{e}$ , i.e. the absence of market demand and difficulties in organisational environment, as evidenced in the descriptive analysis. This justifies further discussion of these conditions.

Organisational environment can be split into two components, when thinking about the mechanisms acting to contribute towards success or failure. Firstly, within small firms, issues tend to be associated with resource allocation, mainly in accessing finance for small firms (e.g. in TransMID), regulatory expertise (e.g. in Prolarix) or vulnerability to takeovers (e.g. in TransMID and banoxantrone). Secondly, interfirm issues can be further categorised between those associated with M&A, the revaluation of projects in light of

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<sup>140</sup> QCA expression from solution 2a and 2b (Chapter 8)

acquisitions, and the associated lack of objective evaluation in small firms pre-M&A, and in the post-M&A integration process in the enlarged firm.

The small firm dilemma, of diminishing cash resources and difficult financial environments, is widely discussed and acknowledged (Martin et al., 2009, Hopkins et al., 2013). As mentioned in Chapters 2 and 3, we observed this to be the case for firms since the 1990s when high profile failures occurred and VC and stock-market interest in the UK biotech sector waned (Hopkins et al., 2013). This has previously been found to effect the ability of firms to take projects through to later drug development (ibid). This thesis confirms this finding, drawing on evidence from a project level perspective.

The organisational environment issues surrounding small firms are inherently linked to the frequency and impact of M&A. In the impact of M&A and licensing transactions, in contributing towards organisational difficulties for small firms, we increasingly witness funding as a key contributor (Hopkins et al., 2013). These events can lead to the definitive termination of a project supporting the literature observing M&A as a disruptive force for the firms involved (Hitt et al., 1991b, Hitt et al., 1991a, Ernst and Vitt, 2000, James, 2002). In addition, this stems from the difficulties in transferring knowledge, in particular from outside the firm.

This thesis highlights that projects in small firms are adversely effected by funding issues contributing towards increasingly frequent M&A causing disruption and delays. This is a key finding for this thesis as it takes the project at the centre of the analysis and provides a novel insight into the multiplicity of organisations involved in the life-cycle of a drug. Alternatively, where supportive environments stemming from the action of key individuals (see section 9.2.3) or, for instance, supportive interfirm collaborative relationships, projects are positively impacted and development is facilitated.

### **9.2.2 Project Drag and Protected Spaces**

As previously mentioned, by taking a project-level approach, this thesis facilitates a relatively unique insight into the dynamics surrounding the progression of drug development. The term 'project drag' has been introduced in this thesis to describe the loss of momentum in drug development, as a result of the accumulation of issues in drug development. In some cases, mechanisms are implemented to counteract this process, however, it can also lead to project termination. Project drag can accumulate in an observed, or latent manner, depending on the action of protected spaces.

As opposed to go/no-go decision-making, project drag relates to smaller issues that independently would not cause termination of development, but are amplified when found in the presence of other negative occurrences.

We draw on the sociology of expectations literature to explain the role of protected spaces, as mentioned in Chapter 3. Protected spaces form when individual expectations are shared across groups. Here, collective expectations around a project are embedded, contributing towards the implementation of subjective criteria for, or the suspension of, evaluation processes (Konrad, 2006).

Furthermore, protected spaces exist at varying levels within and between different teams involved in a drug project. In a larger company, where there are multiple teams working on one project, it may be harder to build up protected spaces between these teams. Furthermore, in a big pharma environment in which there tend to be less limitations in access to the resources, skills, and knowledge required to successfully bring a drug to market, dynamics internal to the project act on decision-making and evaluation processes. Here it was common to witness the accumulation of issues that negatively impact project survival. These include: inadequate level of efficacy, poor strategic fit, low market demand and short patent life. We term such accumulation 'project drag', where negative issues contribute towards a loss of momentum eventually leading to no-go decisions. The observation of this phenomenon implies that success in innovation arises from the alignment of components and how positive and negative effects interact to produce an outcome.

In small firms protected spaces are more readily built up as teams work more closely together and witness the work of others in the process. In this thesis, in these types of organisations we also observe the action of project drag, including efficacy questions, delays, small markets and the relative success of a follow-on, that accumulate throughout project development. However, where project drag in larger firms accumulates freely we find that in smaller firms the project is shielded through the formation of a protected space.

Protected spaces, in small firms, are also likely to result from small firms putting "all of their eggs in one basket". Firms may create a protected space around the project due to the support previously committed to that project and a lack of alternative options, introducing a dependence on that drug. This finding is also linked to the literature relating to risk aversion (section 3.2), and the constraints of firm size, resources and capabilities. In this, small firms, constrained by limited resources and capabilities, were concluded to implement lower thresholds due to the lack of alternative options available to them. In



contrast, in larger firms, projects are predicted to be subject to higher thresholds due to the availability of a range of opportunities.

When issues occur within a protected space in small firms, there is a perception that the problem can be addressed and overcome, perhaps causing delays but not termination (Konrad, 2006). This implies that where project drag occurs in drug development the loss of momentum lies latent, unrecognised by those in close proximity to the project. However, when the protected space breaks down, for instance, due to M&A, the dynamics of project evaluation changes leading to definitive decisions to terminate development.

We find the breakdown of protected spaces leading to the termination of a project clearly in the cases of TransMID (upon acquisition by Celtic Pharma) and CAT3888 (upon acquisition by AZ). Here, project termination occurs soon after the M&A event where the acquiring firm evaluate the project more objectively, or undertake evaluation where it was previously suspended. At this time, the latent issues contributing towards loss of project momentum are uncovered and acted upon, leading to termination. We also observe the potential that the action of the breakdown of protected spaces may be occurring in the case in the BTG acquisition of Protherics, for Prolarix, and the merger between Transcept and Novacea in the case of banoxantrone.

Alternatively, in large firms, where we find project drag to be occurring on a continual basis, protected spaces may formulate, however, due to the different organisational cultures, and lack of pioneering mentality, the issues associated with a drag are noted and accumulate throughout development. This is in contrast to small firms where problems are perceived as conquerable.

The dynamics of project drag and protected spaces highlights that drugs tend not to be subject to definitive decisions and are more often terminated as a result of a loss of momentum. This is interesting because it highlights that reasons for project discontinuation are not always definitive, and more accurately a process of combination of issues. Furthermore, this counters the perception that some may have, of decision making process as clear-cut. In addition, this finding emphasises the importance of using a QCA which facilitates an appreciation of the multiplicity of different contributory factors leading to the same outcome (equifinality).

We can further conclude that in the aforementioned context of an industry in a state of flux, with one project's drug development increasingly reliant on a number of different organisations, the impact of the loss of momentum, on the transition of a project from

organisation to organisation, could become more pronounced at present and in the future. Furthermore, where costs are increasing, and efficiencies are necessary, there is a need to address the accumulation of perhaps unnecessary project drag caused by inter-organisational movement of projects.

### **9.2.3 Knowledge Dynamics**

One unexpected finding of this thesis is the role of the drug's knowledge base. This is interesting in the context of the shifts described in Chapter 2, where an increasing role of drug-disease-target understanding was emphasised. However, we appreciate that firms are constrained in the accumulation of knowledge and how they use it. On the one hand, surrounding drug projects with an enthusiastic team helps compensate for a lack of knowledge, helping to mobilise the exploration of research streams to fill gaps (gemtuzumab, Campath). On the other hand, knowledge is shown to accumulate in the development of a pilot drug that can be applied to the development of a follow-on, in a lengthy and expensive process of exploring proof-of-concept (CAT3888).

Furthermore, the difficulty in measuring early stage accumulation of knowledge around a project may also explain the insignificance this condition has in this thesis. Here, it may be the case that in all projects investigated, there is sufficient knowledge to take a project through to development and therefore the knowledge base does not play a role in differentiating success from failure at later stages. This needs to be taken into account when generalising from these findings, as investigating the conditions leading to success of projects in earlier phases may indicate the knowledge base to be important.

The findings from this analysis showed that enthusiasm for novelty did help successful projects utilising new therapeutic approaches. However, this was not found to be a necessary or sufficient condition, as it was also witnessed in unsuccessful projects.

Technologies, and, in this study, projects, can be supported through the excitement and desire for new scientific and technological knowledge, operational principles and proof of concept, through the action of project advocates, as explained above. This confirms the relevance and importance of insights from the sociology of expectations literature and, in particular, studies exploring new technological approaches, where advocates mobilise the sharing of visions to form collective spaces between individuals.

The consistency of the research group over time, the cultural practices within an organisation and the complexities in transactions involving the projects, were also found to play a role. This can again be related to the collective expectations surrounding projects and the associated facilitation of knowledge transfer mechanisms. In the former,

research groups working together would be more likely to share visions around a project that would become engrained in working environments and relationships. Furthermore, where individuals work together more readily, the transferral of tacit knowledge will be facilitated by the development of trust, social capital and the associated ease of communication and coordination.

This formation of shared expectations is also clearly linked to the aforementioned concept of protected spaces which form around a drug project in the case where groups work closely together and collectively drive towards a successful outcome for the drug. As was the case for protected spaces, knowledge accumulation is more easily facilitated on a within-team, rather than between-team, basis and therefore, where teams are based on disciplinary silos, it is less likely that the knowledge accumulation and formation of protected spaces will continue through the drug's life cycle and as it progresses from team to team and organisation to organisation.

The accumulation of knowledge through mechanisms of cooperation, communication and coordination show further salience when we consider the multidisciplinary nature of the knowledge utilised in drug discovery and development processes. This multidisciplinary stems from the shift in approach from trial and error, towards one that uses more structure-, or target-based knowledge, as described in Chapter 2. In other words, the accumulation of knowledge surrounding a drug, its target, and disease pathway requires people with unique expertise to come together to transfer and exchange ideas.

#### **9.2.4 Project advocates**

Another key factor drawn out in the descriptive analysis was the role and characteristics of effective project advocates who provided the capabilities to overcome critically detrimental events, such as Elion in nelarabine and Waldmann in Campath.

In Chapter 3 we conceptualised a 'project advocate' as a person who has the skills, expertise and characteristics sufficient to contribute towards differentiating success and failure. For instance, the ability to mobilise resources, both from within the organisation and from surrounding networks. Individuals are likely to become project advocates through a history of involvement and a vested interest in seeing the drug project from conception through to successful launch.

In this dynamic we witness certain types of project advocates to be noteworthy in their action and characteristics. Most commonly these people promote the innovation by utilising their wide-ranging networks and consistent enthusiasm for the project to overcome hurdles in development. Project advocates align resources and skills to counteract the loss of momentum associated with project drag, and issues that would otherwise lead to definitive failure, for instance, following license discontinuation in the case of Campath. In particular, where project drag is compounded by the movement of drugs between organisations, the presence of a project advocate who has the sufficient capabilities to overcome the detrimental impact of these changes, retaining momentum in the drug's development, allows success to be achieved.

Where markets are small, the action of key individuals, managerial support and cooperation act to provide an alternative avenue to motivate resource allocation. For instance, this occurs in the success of nelarabine and gemtuzumab, in the absence of a large expected market demand. In addition, where a project is used for proof of concept, as was seen in gemtuzumab and CAT3888, a smaller market may be accepted given the potential that future projects may have broader applicability. In CAT3888 the knowledge accumulated through the project enabled the development of a follow-on candidate which displaced the drug's development upon AZ's acquisition of CAT.

The role and characteristics of the key individuals identified in this thesis can be related back to the literature explored in Chapter 3. Here Rothwell and colleagues (Rothwell et al., 1974, Rothwell, 1992) emphasise the power, age, seniority and experience of individuals in influencing the impact they have on innovation. In addition, under Tidd and Bessant's (Tidd and Bessant, 2013) characterisation the key individuals in nelarabine and Campath fulfil two or more of the roles described: for instance, functioning as an inventor (with knowledge breadth, and the ability to provide inspiration, motivation and commitment), with proximity to the organisational sponsor (with power, influence and the ability to pull strings), and technological gatekeeper (who is responsible for collecting and distributing information).

The contribution of key individuals is important because it highlights the interpersonal nature of drug development. Here, we perceive there to be integral role for individuals who can promote a drug and thereby facilitate the translation and transferral of knowledge from one firm to another, upon licensing agreements or M&A events. Individuals who have the capacity to use their networks, accessing resources and aligning expectations surrounding a project, are important to drug innovation. This mechanism is predicted to be important, particularly in a context in which the industry is

attempting to overcome productivity issues through consolidation and external access to knowledge and projects.

### **9.3 Policy Recommendations**

The conclusions from this thesis lend themselves to recommendations that can be implemented to work towards resolution of the unnecessary discontinuation of projects with the potential to change patients' lives.

The key recommendations of this thesis are most relevant to managers of organisations and other industry stakeholders. The recommendations are based on the general assumption that, as the pharmaceutical and biotech industry continues to change and shifting dynamics continue to occur, the issues identified in this thesis, particularly around organisational environments, the breakdown of protected spaces and project drag, become more salient. We see an increase in the numbers of inter-organisational movements occurring during a project life-cycle, increasing costs and additional complexity stemming from the shift towards personalisation and the need for involvement from multiple disciplines, teams and organisations, around an individual project.

This thesis has found that protected spaces are generated from the formation of collective expectations shared by those involved in drug development which lead to a shared goal. In some instances, this has been found to have the potential to overcome the accumulation of issues which could otherwise cause doubts over development and lead to termination of the project, so-called project drag. Where we observe that more disciplinary teams and organisations are involved in the development of a drug project, and M&A becomes a critical part of organisational strategy, there is an increasing need to acknowledge the potential for project drag to occur and to maintain protected spaces where the project is strategically important.

Where protected spaces are broken in M&A and therefore do not pass to new organisations or teams, project drag becomes pronounced and can be problematic to the outcome of the drug. M&A, licensing and collaborative agreements should consider the importance of interaction between old and new teams to facilitate the transferral of tacit knowledge and shared expectations surrounding a project. Organisational negotiations around a drug project depend on the shared goals and therefore spending time sharing and setting these out is important. In these types of agreements, which are becoming an increasingly integral part of a project lifecycle, it is necessary for there to be extensive contact between teams, while also accounting for the multitude of teams involved, ranging from scientific to marketing and sales, regulatory and managerial.

The findings from this thesis also support the argument that development teams should, where possible, be retained post-M&A, in order to maintain momentum around projects. Furthermore, if the project is strategically important then the acquiring organisation should focus on understanding the project teams involved and maintaining the protected spaces around them and avoid introducing and imposing new ways of working unnecessarily.

If a collaborative strategy involving partners is required, it should be considered that these multidisciplinary teams should be given the opportunity to develop a deep mutual understanding of the project, with a holistic and shared view of its development, in order to ensure their findings can be taken into and maintained within the protected space.

Where small companies have strategic objectives that involve eventual M&A, this should be considered on the project level in order to account for project drag and the potential breakdown of protected spaces. These would involve accounting for expectations of acquiring companies where data should be recorded as well as efforts made to retain and transfer tacit knowledge. This may require early and prolonged interaction with the acquiring company, something that may be difficult, where small companies are often forced into M&A.

Furthermore, where personalised medicine may require an increasing role for small firms in discovering new and innovative projects, it is necessary for these firms to have the support to remain independent and calls into question the ability and suitability of small firms to be involved in development stages of the lifecycle of a project.

The findings of this thesis surrounding the role of the organisational environment feed into the discussion of whether small firms are capable of carrying out late stage development. This finding supports conclusions from previous studies which also highlighted issues for small firms in accessing sufficient funds for this expensive late stage of drug development (Hopkins et al., 2013). Here, the small firms that provide an important source of new projects for the industry, cannot satisfy their essential role unless they are sufficiently capitalised, in order to help provide a shield to industrial dynamics.

Small firms need to access funds but also not raise capital at a valuation of detriment to their shareholders. One problem is the difficulty in valuing and promoting the worth of early stage products. This could be facilitated by the second policy recommendation of this thesis, namely in the alignment of the needs of patients with projects early in development.

The ability for firms (big and small) to formulate markets and package products to be attractive and accessible to potential patients and partners, facilitates the coordination and cooperation necessary for product development.

One way of early acknowledgement of the potential market of a project highlights a role for patient groups. Patient groups, in rare disease communities, commonly bring together patients and drug development R&D. Despite being expected to appear in this thesis (in rare cancers) the involvement of patient groups was not found to be significant. This may be a function of the midline rarity of the 'rare' cancers, whereby the diseases may be more associated with cancer, which are commonly well-researched, than rare diseases. However, lessons can still be learned from rare cancers that might be applied on the advent of the molecularisation of oncology in therapeutics, and in personalised medicine.

In rare diseases, patient groups play an important role by articulating their demand for treatment options (Boon et al., 2008, Moors et al., 2008, Boon et al., 2011). This connection, between users and producers, may also be beneficial for firms to gain access to, and support from, the patients who comprise the market they aim for. However, where patient groups often rely on the lumping of diseases together into categories, the molecular understanding of cancer and the increasing interest in personalised medicine may act in the opposite direction, splitting diseases and therefore making the sharing of visions and expectations harder.

This thesis indicates that there should be an increase in communication between patients, and organisations involved in the drug innovation process should, however, also be considered in the context of the 'patient revolt' as described by Vasella and Slater in the narrative around Gleevec (imatinib) (Vasella and Slater, 2003). In this case the firm may be hesitant due to issues surrounding manufacturing scale up and the action of patients lobbying for the drug. Therefore, caution should be implemented in involving patients in the drug development process.

Firms should be more involved in accessing and formulating their markets during early phases of drug development is contentious whereby population increases have been exploited through consumerism, promotion and 'pharmaceuticalization'<sup>141</sup> (Abraham, 2010). However, here there is a positive perspective where we consider the potential that even in the context of low potential market demand, the ability to link drug

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<sup>141</sup> 'Pharmaceuticalization is a term developed by Abraham and colleagues to describe the influence of the pharmaceutical industry on politics, markets and society, in general.

development with patients at earlier stages could be mutually beneficial to both firms and patients<sup>142</sup>.

The existence of project drag and protected spaces implies a need for more understanding, cross organisationally, between small firms and large firms as to the way in which projects should/can be assessed and understood. We acknowledge that large firms tend to be the market for small firms, therefore projects initiated in biotech need to be more geared to the evaluation criteria imposed upon them by pharma. However, there is a danger of the occurrence of collective denial, wherein small firms would benefit from opening themselves and projects up for criticism to avoid group-think.

In addition, big pharma could learn to be more sympathetic to the needs of patients and smaller firms, where projects suffer from project drag and vulnerabilities to industrial dynamics. Due to the different specialisations and expertise of big and small firms, it may be the case the projects from pharma may benefit from being licensed to smaller firms for development, as opposed to termination. This was demonstrated in the SUGEN-AZ agreement where the smaller company had the opportunity to take on development of the projects, should AZ terminate their development for economic reasons. This appreciation for the distinction in the thresholds imposed by different sized firms and the necessity for the processes to be aligned is important and could contribute towards the development of more drugs for patients.

#### **9.4 Methodological Contributions**

Another contribution of this thesis is methodological. This is in the framework and its operationalisation, and the combination of multiple case study research with a QCA, with a theory-building objective. Despite the existence of the four conditions in other studies, such as Moors and Faber (2007), the way in which these have been operationalised and data gathered, largely from publicly available sources for this thesis is unique. This is due to the in depth and systematic range of data the present case studies draw on. This allows for a level of cross-case comparison that would not be possible in a scenario where data are taken from personal accounts only.

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<sup>142</sup> Pricing is a complex and evolving issue, subject to a variety of dynamics applied to different contexts. There is not space to discuss these issues in this thesis, which, furthermore, rely on marketing and adoption strategies, going beyond the issues associated with development. In addition, as demonstrated in footnote 87, pricing is subject to high levels of uncertainty, and is unpredictable, even by the firms responsible for drug commercialisation.



In addition, the multi-dimensional approach undertaken, with the project at the centre of the analysis, has proved to be valuable in appreciating the extent to which projects can frequently move from organisation to organisation. This has allowed for an appreciation of standalone projects without limiting the analysis within the organisational boundary, thereby allowing a picture to be built up of the development of the drug from start to finish.

The methodological approach employed here has also facilitated a well-rounded discussion of success and failure, whereas in prior research the focus has tended to be on one or the other. The QCA allowed us to analyse these scenarios separately and in comparison, facilitating a more realistic picture of an outcome, whereby the absence of an outcome is not necessarily conducive to the opposite causal pathway explaining the presence.

## **9.5 Limitations**

Despite the interesting insights garnered from this thesis it is also important to consider these in the context of certain limitations. For instance, the conclusions presented here can be critiqued due to the potential for endogeneity between conditions. Here, in particular, there is a possibility of reverse causality between the outcome and supportive organisational environment, whereby the failure in the project may lead to the breakdown in the environment surrounding that environment, rather than the causal direction outlined previously. Here it is logical that the issues with the organisational environment observed in this thesis, e.g. funding, delays in development and M&A, may be seen to stem from the lack of potential of a project to succeed. However, this is interesting to consider as it is the perception of these factors that is ultimately at issue, bringing the discussion back to issues of evaluation criterion, expectations and protected spaces in firms and the role of individuals in contributing towards these.

Another limitation stems from the amount of data that it has been possible to collect while compiling 11 cases. In order to establish a breadth of data for a range of cases, by necessity the depth of the case histories presented in this thesis has been reduced. This was in part overcome by the involvement of interviewees in previewing the case histories. Here, interviewees had the opportunity to read the case studies generated from publicly available data, prior to the interview. In addition, interviewees were sent the relevant case history when it had been completed, in order to verify the information presented. While only five interviewees replied giving approval, in general there was an agreement of the quality of the case studies whereby only small clarifications were volunteered in some instances. The main purpose of this was to ensure that the representation of the

case history was in line with their recollection. However, it is always possible, in any research, that there is important information that has not been considered.

In addition, this thesis has not explored the dynamics of post-approval marketing and commercialisation efforts, and in most instances there has not been space to establish or comment on what happened to the projects in the adoption phases. For this reason, the definition of success is imperfect as commonly drugs cannot be observed as being successful until they have reached the patients' bedsides. However, for the purposes of this thesis, where the aim was to understand more about the events leading up to approval, the definition of success used was sufficient.

## **9.6 Further Research**

The final limitation of this thesis is its focus on rare cancers. This also provides an avenue for further research. Here we admit that the insights concluded from the case histories and analysis can only be applied more broadly with caution, both in rare diseases and drug development more generally. With consideration of this further research investigating the dynamics of other rare diseases would also be warranted. Furthermore, in time, when drugs developed for personalised medicine are more widespread it would be interesting to assess whether they suffer from the same issues, and development pathways to those that have been identified here.

In addition, where new policies have been introduced to attempt to overcome the market failure in the area of neglected diseases, the application of the methodology and framework highlighted in this thesis may provide a productive avenue for investigating the dynamics in this area. The prediction would be that, due to the lack of interest in this area finding sufficiently comparable cases would be problematic, however, in time this might be overcome. There may be an impact, for instance, in the case of neglected diseases, on the dynamics of protected spaces and project drag. Here policies such as advanced market commitments, which have been suggested to motivate the development drugs with the incentive of a predetermined guaranteed market, may enhance the protected space surrounding the development of a drug through the sharing of a vision contributing towards the suspension of evaluation criteria.

## **9.7 Summary and Key Conclusions**

In summary, this thesis has contributed empirically, methodologically and theoretically, as well as suggesting policy resolutions, and advancing our understanding of the drug development process. Empirically, we have mapped out the environment surrounding drug innovation in rare cancers highlighting the frequent movement of projects between

organisations and the multiplicity of the actors involved. This finding was facilitated by the implementation of a novel method that furthered the discussion of drug innovation, in providing a comparative analysis of a medium N set of case studies.

Theoretically, this thesis has highlighted a causal complexity that exists in the development of drugs, whereby successful drugs are the product of a process involving the alignment of components that contribute in differing ways, dependent on context. We have found that it is difficult and expensive to produce drugs but that with perseverance and the right external and internal environmental selection pressures, projects can succeed despite project drag and adverse events. However, for projects originating in small firms, where there is a vulnerability in accessing resources, success is dependent on the sufficient survival of the organisation and the impact of the environment surrounding the firm.

We recommend policies and considerations to address these issues. Firstly, in improving the environment for small firms to enable the support of projects, and the alignment between large firms and small firms, who are mutually dependent. We observe that there may be benefits to the action of market access and creation early on in drug development, both for patients who gain access to important therapeutics, and to the firms developing them. This is anticipated to be more challenging given the shift towards personalised medicine and the associated splitting of disease areas.

It is anticipated that this thesis provides a starting point for the systematic, comparative and cumulative assessment of the successful development of drugs. Future work, involving investigations into alternative disease classes may emphasise different causal pathways, however, this thesis provides a foundation for these assessments. This addresses a dearth in the current literature whereby small N or single case study research is seen alongside large studies showing broad trends. By providing an avenue by which research can fulfil a middle ground, this thesis aims to provide a shift from anecdotal evidence to conclusions based on comparative analysis unpicking the internal structure of causality.

## Appendix 1

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Interviewee A = John Tite

Former Department Head, Therapeutics Section, Wellcome Foundation (1990-1995)

Interviewee B = Doug Onsi

Former Chief Operating Officer, LeukoSite

Interviewee C = Dr Chris Mirabelli

Former Chief Executive Officer, LeukoSite

Interviewee D = Dr Richard Youle

Senior Investigator, National Institute of Neurological Disorders and Stroke

Interviewee E = Anonymous

Interviewee F = Professor Stephen Taylor

Formerly at Faculty of Life Science University of Manchester

Interviewee G = Dr Patrick Round

Formerly Senior Vice President at Cambridge Antibody Technology

Interviewee H = Professor Laurence Patterson

Formerly at De Montfort University and School of Pharmacy, London

Interviewee I = Dr Geoff Yarranton

Formerly Director of Research, Celltech

Interviewee J = Professor Ian Judson

The Institute of Cancer Research, Royal Marsden, Sutton

Interviewee K = Anonymous

Interviewee L = Udai Banerji

The Institute of Cancer Research, Royal Marsden, Sutton

Interviewee M = Anonymous

Email correspondence X = Dr Russell Hagan

Head of R&D at British Technology Group

Email correspondence Y = Anonymous

Email correspondence W = Dr Joanne Kurtzberg

Department of Pediatrics, Duke University

Email correspondence V = Professor Malcolm Stevens

Formerly at Aston University

## Appendix 2

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### Interview Questions

These questions were used by the interviewer but generally not presented to the interviewee unless requested.

- What was your role at [firm name]? How did you first become involved in the project and what was your continued involvement in the project?
- Can you say something about the initial scientific research that contributed towards the origins of the project?
- Was it discovered in-house or licensed in?
  - o Involvement of original investigators?
- What was the target market for the drug project initially? Did it change, and if so, why?
- What role did this demand play in discussions around the project? For instance was it always the intention to develop the project for multiple indications? Or was there a reliance on high prices or the incentives gained from orphan drug designation
- Can you tell me a bit about the science behind the project?
  - o e.g. novelty? Controversy? Still in development?
- Did patient groups or charities play a role in the development of the project?
  - o What role did this demand play in discussions around the project? For instance was it always the intention to develop the project for multiple indications? Or was there a reliance on high prices or the incentives gained from orphan drug designation
- To what extent was the project part of a wider firm strategy?
  - o – in rare diseases, - in cancer, - in personalised medicine?



University of Sussex

SPRU – Science Policy Research Unit

**Participant Consent Form**

***Why do some drug projects succeed in development and others fail? A study to understand the conditions for which drugs for rare cancers are developed***

1. I confirm that I have read and understood the information sheet provided for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal right being affected.
3. I understand that the digital recording of the interview is voluntary and that I am free to decide whether to allow it.
4. I understand that my response to the interview question will be used for research purposes and for this particular research project specifically.
5. I understand that the association of my interview responses with the organisation I was working with at the time of interest is voluntary and that I am free to decide whether to allow for this association.
6. I agree to take part in the above study.

.....  
Name of participant

.....  
Date

.....  
Signature



### **Participant Information Sheet**

#### ***Why do some drug projects succeed in development and others fail? A study to understand the conditions for which drugs for rare cancers are developed***

I would like to invite you to take part in a doctoral research study. Before you decide whether to take part I would like to give you the opportunity to understand why the research is being done and what it would involve for you. Please take the time to read the following information carefully, with thanks in advance.

This research project is part of my PhD research into drug innovation for rare cancers. The research project aims to inform both policy and industry by identifying the socio-technical conditions that lead to successful drug innovation, particularly in drugs for cancers that affect small populations ('rare cancers'). If you are interested in receiving the results of this research please let me know and I can send you a copy.

The research will be implemented by collecting data on case histories, where a case is defined as a drug project developed for a rare cancer (whether successfully approved and launched, or discontinued in development). Areas for data collection are 1) market demand, 2) knowledge base, 3) stakeholder perception, and 4) firm synergies. A large majority of the relevant data has been gathered using desk-based research techniques, by accessing publicly available databases. The specific types of data already collected include: whether the drug had orphan status, which indications were being explored and how common those indications are, any mention of expectations of market potential in industry press releases/newspaper articles, publication analyses of the primary indication and target, the number of relevant patient groups (for the primary indication), the expectations of the drug as presented in newspaper articles, and the nature of the firm involved in development (e.g. size, previous experience and M&A activity). It is felt, however, that discussing the process of drug development with those involved will add an extra dimension to the research.

The interviews that will be carried out involve contacting various stakeholders involved in the drug discovery and development process, to fill in the gaps in the story on an ad hoc basis and to add depth to the analysis. In addition, I am also interested in more general discussions surrounding the decision making processes and risk-management strategies within both public and private organisations.

Participation in the interview is entirely voluntary and you are free to withdraw at any time. I will ask you to sign a consent form to show you have agreed to take part.

Interviews may be recorded using a digital voice recorder, however please let me know if you are not comfortable with this. For contextual reasons it may be useful for me to be able to associate your answers with the organisation with which you were associated during the drug project discovery or development, however if it is your expressed wish for this not to be the case please let me know. Otherwise, all interviews will be anonymised.

This research has been periodically reviewed by my doctoral supervisors (Michael Hopkins and Paul Nightingale), and the research committee of my academic department at the University of Sussex. Furthermore, the research has received approval from the University's ethical review process.



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